Journal of AIDS and HIV Research

Volume 9 Number 1 January 2017
ISSN 2141-2359

Academic Journals

ABOUT JAHR

The Journal of AIDS and HIV Research (JAHR) is published monthly (one volume per year) by Academic Journals.

Journal of AIDS and HIV Research (JAHR) is an open access journal that provides rapid publication (monthly) of articles in all areas of the subject like the implications for gender-based HIV and AIDS prevention interventions, Sputum cellularity in pulmonary tuberculosis, Comparative tolerability and efficacy of stavudine 30 mg versus stavudine 40 mg in patients on combination antiretroviral therapy, HIV and sexual risk behaviours amongst intravenous drug users etc.

The Journal welcomes the submission of manuscripts that meet the general criteria of significance and scientific excellence. Papers will be published shortly after acceptance. All articles published in JAHR are peerreviewed

Contact Us

Editorial Office: jahr@academicjournals.org

Help Desk: helpdesk@academicjournals.org

Website: http://www.academicjournals.org/journal/JAHR

Submit manuscript online http://ms.academicjournals.me/

Journal of AIDS and HIV Research

Table of Contents: Volume 9 Number 1 January 2017

ARTICLES

academicJournals

Vol. 9(1), pp. 1-7, January 2017
DOI: 10.5897/JAHR2016.0398
Article Number: 21B2A5762097
ISSN 2141-2359

http://www.academicjournals.org/JAHR

Journal of AIDS and HIV Research

Full Length Research Paper

A study on HIV knowledge and preventive behavioral practices among FSW'S in Mumbai

Adithyan G. S.[1*], Bal Rakshase[2] and Anna Mia Ekström[3,4]

[1]School of Health Systems Studies, Tata Institute of Social Sciences Mumbai: 400088 Maharashtra, India.
[2]Centre for Health Policy, Planning and Management, School of Health Systems Studies, Tata Institute of Social Sciences, Mumbai: 400088, Maharashtra, India.
[3]Department of Infectious Diseases, Karolinska University Hospital, Huddinge, 141 86 Stockholm, Sweden.
[4]Department of Public Health (Global Health/IHCAR), Tomtebodavägen 18A, Karolinska Institutet, 171 77 Stockholm, Sweden.

Received 11 October, 2016; Accepted 22 November, 2016

The prevalence of HIV among female sex workers (FSW) in India is highest in the state of Maharashtra (7.4%). Mumbai, the capital city of Maharashtra, with a large sex industry mainly consisting of brothels, lags behind in the overall average decline in HIV seen in this state over the last decade. Condoms are now widely used by sex workers through the pro-active role of Mumbai District AIDS Control Society (MDACS) and many non-governmental organizations (NGOs), but many associated risk behaviours remain and contribute to the high HIV prevalence among FSW in Mumbai. This community-based descriptive study was conducted to assess HIV/AIDS-related knowledge and sexual risk behaviours among FSW in Mumbai in 2015. Knowledge was assessed using a 'cumulative knowledge score' by taking 18 questions to assess HIV/AIDS knowledge. Sexual behavioural practises among FSW with occasional clients, regular male clients, regular non-paying male partner and non-regular non-paying clients were also assessed separately. Ninety-one FSW working in brothels in Mumbai gave informed consent and were purposively selected to participate in the study. The mean age of the respondents was 32.9, three out of four were illiterate and 62% were either married or had a live-in partner. 85% of the study population reported above average satisfactory score (score≥8) on cumulative knowledge on HIV/AIDS and a nearly 100% used condom both with regular and occasional clients. The study revealed some risk factors among FSW and their regular non-paying partners that need to be urgently tackled. Most of the FSW (86%) use more than one condom during a sexual act, and it was also found out that they tend to engage in risky sexual practices with their regular non-paying partner without condom, thinking that it was not necessary.

Key words: HIV, female sex workers, knowledge, risk behaviour, condom use, India, Mumbai, brothels.

INTRODUCTION

Globally, India hosts the third-highest number of people living with HIV (PLHIV) in the world, over 2.1 million despite a very low prevalence rate of HIV (2.9%) in the general population (NACO, 2016a). Seven states in India account for two-thirds of the total number of PLHIV in the country, including the state of Maharashtra with over 310,000 PLHIV (NACO, National Institute of Medical Statistics (NIMS) and ICMR, 2016). India has seen an overall reduction of 66% in new HIV infections over the last decade, from 270,000 new infections in the year

2000 to 86,300 in 2015 (NACO, NIMS and ICMR, 2016). It is assumed that this reduction is a result of various targeted interventions and scaled-up prevention strategies under the National AIDS Control Programme (NACP) (NACO, 2015). The number of AIDS-related deaths has also declined after a decade of access to antiretroviral therapy (ART), introduced in 2004 and scaled-up throughout the country. However, only an estimated 35% of PLHIV are on first-line ART (747,000 in 2014) at 519 ART centres across the country. These make up 50% of those diagnosed. Thus the majority of PLHIV in India are not yet on ART and still do not know their HIV status (WHO, 2015).

An important route of transmission in India is the sex industry, which includes a large number of people with high-risk behaviours, especially in areas with large urban populations. Female sex workers (FSW) and their clients belong to the core high-risk groups in India (NACO, 2015). Recent studies estimate that the number of sex workers in India range from 860,000 (NACO, 2015) to 3 million (Dasra, 2013). The most recent National Integrated Biological and Behavioural Surveillance from 2015, showed that 90% of FSW had been exposed to one or more HIV-related services during the 12 months prior the survey and that the HIV prevalence among FSW at national level has declined considerably over the last years, from 5.0% in 2007 to 2.2% in 2015 (NACO, 2016b).

Only six Indian states (Maharashtra, United Andhra Pradesh, Manipur, Mizoram, Nagaland and Karnataka) have HIV prevalence above 5% among FSW (NACO, 2016b). Maharashtra has the highest prevalence of HIV (7.4%) among FSW, more than 23 times the state's general population (0.32%) (NACO, 2016b). Over 14% of all women in the commercial sex industry in India work in Maharashtra (Dasra, 2013). In Mumbai, the capital city of Maharashtra where the largest brothel-based sex industry in India is located, the HIV prevalence among brothel-based sex workers has remained high or even increased (28% in 2007 to 35% in 2009) despite preventive interventions at the national level (ICMR and FHI 360, 2012) . As a result of the proactive role of peer educators and Non-Governmental Organizations (NGOs), knowledge levels of HIV have increased and behaviours have changed. Condom use is now widely practiced among FSW but the mean number of clients per week for FSWs in Maharashtra is 16.7 higher than in all other states (Adhikary et al., 2012). This indicates the pitfalls in current preventive strategies also given the consistently high number of new HIV infections. The current main strategy of India's Phase 4 prevention programme (2012-2017) is to expand information, education and communication services with a focus on behavioural change among FSW (NACO, 2015). The purpose of this study is to assess the knowledge of HIV among FSW and the extent to which this knowledge has been translated into actual preventive behavioural patterns in this key population something which is of high importance for controlling the HIV epidemic in India.

METHODOLOGY

The research was a community-based cross-sectional descriptive study design to collect interview data from 91 brothel-based FSW from January to March 2015. The respondents were identified using purposive sampling technique. The brothels were conveniently selected from three different brothel areas in Mumbai based on key informant (outreach workers) suggestions from NGO. The inclusion criteria were: Being a brothel-based FSW aged 18 to 50 years located in Mumbai. FSWs aged below 18 and above 50 were excluded from the study

A pilot study was carried out among ten respondents using semi-structured questionnaire to test the feasibility of the study and to finalize questionnaire. A structured face to face interview was conducted by a male researcher (first author) in a private room within the NGO facilities. The average duration of the interviews was 20 min. There was less than 2% non-participation rate which includes respondents who interrupted in between the interviews due to unwillingness to answer the questions.

The questionnaire was divided into three main parts: Socio-demographic profile, knowledge regarding HIV and actual HIV preventive behavioural practices. There were 67 questions in total including 20 questions to assess knowledge of HIV/AIDS. The knowledge section was again sub-divided into general awareness, knowledge regarding transmission, misconceptions and knowledge regarding treatment. Response options included: Yes/no/don't know/don't want to answer. The "don't know" option was always coded as an incorrect as it also denotes that the respondent is unaware/ lacks knowledge on that aspect of HIV. A self-constructed cumulative knowledge score instrument measured the knowledge about HIV/AIDS. It was created by adding up the number of correct answers (1 point per correct reply/0 for incorrect or don't know) to 18 selected questions. The maximum score was thus 18 and the minimum was 0. The range of scores were classified into unsatisfactory (0 to 3), below satisfactory (4 to 7), satisfactory (8 to 11), above satisfactory (12 to 15), and, high knowledge score (16 to 18).

There were 35 questions on sexual behavioural practises among FSW with once-off/ occasional clients, regular male clients who pays, regular non-paying male partner (husband, live-in-partner, lover or boyfriend) and non-regular non-paying clients (police, pimps, etc.). Health seeking behaviour of the FSW was also assessed in this section. A descriptive statistical analysis was done in the study and no inferential statistical tests were used, mainly due to the low sample size.

Ethical clearance was sought from the School of Health Systems Studies, Tata Institute of Social Sciences, who were part of the Institutional Review Board (IRB). The approval and consent from the NGOs working in this area were also taken before the study. Written informed consent was taken from all the study participants before study. All personal information of the respondents such as name and the area are kept anonymous and confidential in locked compartment, accessible to the first author only. All questions had a

*Corresponding author. E-mail: adithyangs@gmail.com, adithyan.suresh2014@tiss.edu. Tel: + 91-7506209769/ 9037710290

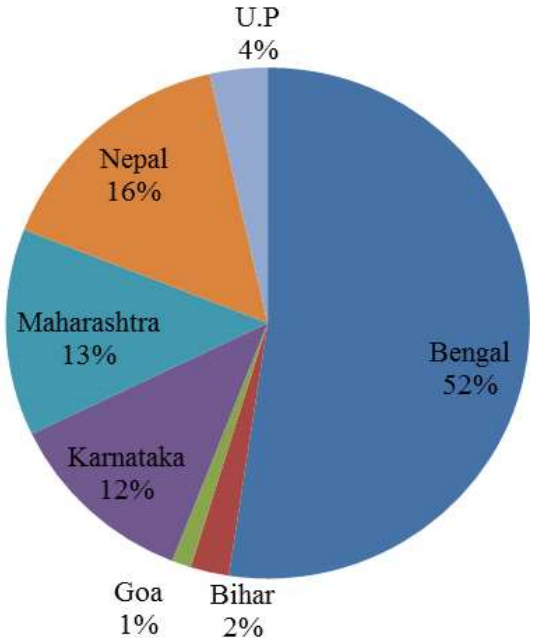

Figure 1. Native state of FSW participated in the study (N=91).

"don't want to answer" option, and the interviewees were informed that they were free to interrupt the interview or refuse to answer any question without any negative consequences. The study participants were not given any monetary incentives for participating in the study.

FINDINGS

Socio-demographic profile

Out of the 91 respondents, the majority of the FSWs (52%) came from West Bengal, followed by Nepal (16%) and the Indian states of Maharashtra, Karnataka, Uttar Pradesh, Bihar and Goa (Figure 1). The socio-demographic characteristics of the respondents are shown in Table 1. The mean age was 32.9 years; the majority were Muslim, and 62% were either married or had a live-in partner. Three out of four respondents were illiterate, and 80% of the women earned between 0.5 and 5 USD per day (15 to 150 USD per month). Most of the FSWs had their first sexual debut at a very young age (70% had before 18 years).

HIV testing and status

All the respondents (100%) had done at least one HIV test. Slightly over half (52%) had been tested at their initiative while the rest had been tested by NGO members who came by the brothels to offer HIV screening. All the FSWs (100%) also knew their HIV test results. The prevalence of HIV infection among study population was 7.6% (7/91 self-reported cases) which is higher than the national and state prevalence rate. This information was collected from previous test results and cross checked by principal investigator. Most of the FSWs said they went for HIV screening once every three to six months, but more than 50% of the respondents were unaware of their regular non- paying partner's HIV status, and only 56% of them asked about the HIV status of clients.

For most of the respondents, sex work was their main source of income, and only 7% had other jobs apart from sex work. Even though 62% have/had their husband or live-in-partner, only 25% of the FSW received any financial help from their live-in partner or husband. The mean duration of sex work was 11 years, and most of them planned to continue in the profession to take care of their children. Ninety percent of all interviewed FSWs had at least one child. The most common reason for entering into sex work was poverty and the need to contribute to household expenses; the second most common reason was having been forced into sex work by others (Figure 2).

Knowledge

All the respondents in the study had heard about HIV/AIDS, but all of them had received this knowledge from an NGO and not from government sources. Most of the respondents were aware of common modes of transmission, and also about treatment for HIV/AIDS. The main knowledge gaps included how to access treatment, breastfeeding as a mode of transmission and whether HIV can be transmitted through sharing a meal or through coughing and sneezing. The complete descriptive statistical analysis of the knowledge analysis is given in Table 2.

Cumulative knowledge analysis

The self-constructed cumulative knowledge score instrument yielded the following findings. It was revealed that 35% of the respondents had high knowledge and 84% had a cumulative knowledge score above the 'satisfactory' level. About 16% of respondents fell in the unsatisfactory category. The cumulative knowledge level among FSW's regarding HIV/AIDS is represented in Figure 3.

Behavioural practises

All the respondents bought their condoms free of charge from an NGO (associated with MDACS), and almost 90% were comfortable with this. All respondents were satisfied with the current supply process of condoms through NGO

Table 1. Socio-demographic characteristics of female sex workers in Mumbai (N=91).

Parameter		N	%
Age* (years)	≤30	54	59
	>30	37	41
Religion	Hindu	42	46
	Muslim	48	53
	Christian	1	1
Marital status	Married	44	48
	Live-In partners	13	14
	Separated /divorced	22	24
	Widowed	8	9
	Single	4	5
Children	No	9	10
	Yes	82	90
Education	Illiterate	66	73
	Primary	13	14
	Secondary	12	13
Monthly income (Rupees)	1000-10000 (15-100USD)	73	80
	10001-20000(151-299USD)	14	15
	20001-30000(300-450USD)	4	5

*The mean age (years) of the sample is 32.9 (SD= 7.2).

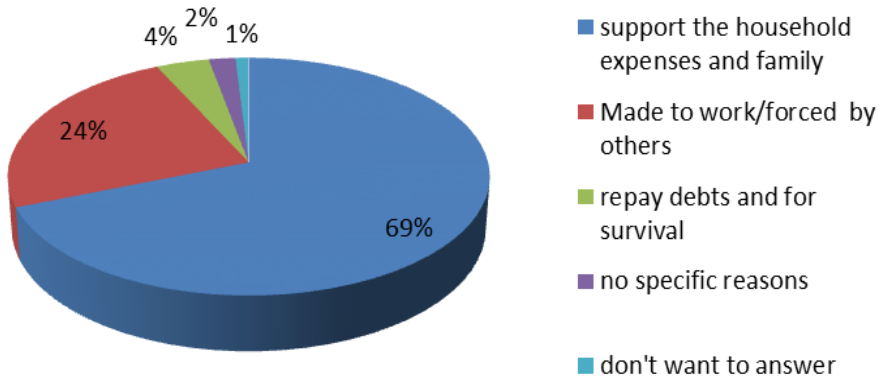

Figure 2. Reasons given by FSW for entering into sex work (N=91).

and had never faced condom shortage.

More than 95% of the respondents had used a condom at every sexual intercourse with occasional clients during the last three months. The respondents reported a 100% condom usage during the last sexual act (last one month). Most of the time (in 87% of the cases), the FSW initiated condom use, and she was the decision-maker. A similar pattern was seen regarding condom practice with regular clients. Thus, both with occasional (once-off) clients and regular paying clients, the FSWs consistently used condom.

In most of the cases (96%) respondents also said they were able to refuse sex if the client refused to use condoms without any second thought. The rest said that they used female condom during this scenario. This reflects an increased awareness among them about the

Table 2. Knowledge of HIV/AIDS among FSW in Mumbai, India (N=91).

Statements	Yes (%)	No (%)	Don't know (%)
A healthy-looking person cannot be infected with HIV, the virus that causes AIDS	24	56	20
HIV reduces our immunity to fight against infections *	54	3	43
Correct and consistent condom use is the best method of HIV prevention	97	0	3
People can protect themselves from HIV/AIDS by having one uninfected faithful sex partner	68	3	29
Having sex with more than one partner can increase a person's chance of being infected with HIV	76	4	20
A person may get HIV/AIDS by getting injections with a needle that was already used by someone who was infected	89	2	9
Receiving a transfusion, with blood infected by the AIDS virus, is one way to get the disease	83	2	15
A person may get AIDS by sharing a needle with a drug abuser who has the disease.	75	15	14
A pregnant woman infected with HIV or AIDS transmit the virus to her unborn child	80	7	13
A woman with HIV or AIDS transmit virus to her new born child through breast feeding	63	16	21
A person gets HIV/AIDS by sharing a meal with someone who was infected	23	63	14
Coughing and sneezing do not spread HIV	56	26	18
A person get HIV/AIDS from mosquito bites	27	54	19
A person can get HIV by sharing a glass of water with someone who has HIV	27	56	17
If you shake hands with someone who has AIDS you can get the disease	11	71	18
There is clinical treatment available for HIV	67	8	25
Ever heard of ICTC (Integrated Testing and Counselling Center) -where one can get information on HIV/ AIDS and get tested for HIV/AIDS*	75	5	20
Ever heard about ART Centers-where one gets medicines for HIV/AIDS*	46	10	44

*For all the statements with a * mark, the sample size is 90 (N=90).

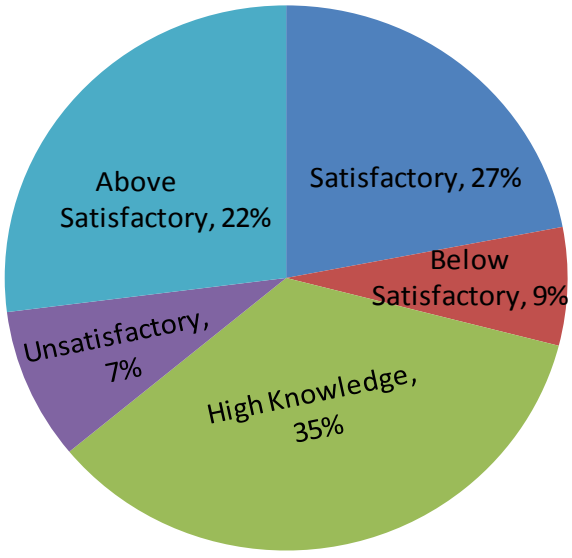

Figure 3. Pie-chart showing percentage of FSW belonging to each knowledge category (N=91).

importance of condom usage and also empowerment among FSW regarding the decision-making process.

The relationship between knowledge about condom use and actual number of condoms used between the FSWs and clients per sexual act was also looked upon. Nearly 97% of the respondents were aware of the fact that condom use can prevent HIV transmission, but only 14% practised appropriate condom use, that is, one condom per sexual act. The remaining 86% FSWs knew that condoms prevent HIV infection, but preferred and allowed the client to use more than one condom per sexual act (one on top of the other) which is a faulty practice. The FSWs had been informed by their peers and NGO workers about correct condom use, but they were still worried that using one condom could increase the risk of transmission due to possible tearing of the condom and therefore preferred to use two or more condom since they believed this would enhance protection.

Sexual practices with regular non-paying partners (Table 3), including husbands, live-in partner, lovers, boyfriends etc. were quite different compared to those practised with clients. Sixty-four percent (N=58) of the respondents had a regular male partner who did not pay for sex. Among this category (N=58), 36% of those with regular non-paying partner knew that their partner had another partner while 14% felt uncertain whether their partner also had other partners.

Despite the high prevalence of multiple partnerships

Table 3. Sexual practices of FSW with regular non- paying partners (N=58).

Sexual practices with regular non- paying partner (N=58, 64%)		Percentage
Condom Usage during last sexual act (1 month)	Yes	22
	No	76
	No sexual intercourse with partner	2
Decision-maker in condom use	Joint decision	64
	Decision taken by women herself	36
Condom usage during last three months	Never	57
	Sometimes	24
	Most of the time	14
	Every time	3
	No sexual intercourse with partner	2
Reason for not using condom	Partner objected	16
	Used other contraceptives	3
	Didn't feel it is necessary	79
	Others	2

among the regular sex partners, more than half (57%) of the respondents said they had never used a condom during sex with their regular non-paying partners in the past three months. Only three percent of the respondents used a condom every time. Three-quarters (76%) of respondents had not used a condom during their last sexual act with a regular non-paying partner over the last one month.

With their regular non-paying partners, these women had much less decision-making power than with clients. Only 36% FSWs reported that decision about condom use was taken by her and in rest of the cases the decision was taken jointly with the partner. Also, 79% of FSWs informed that condoms were not used consistently (last three months) with regular non-paying partner since they thought it was not necessary to use condom during a sexual act with husband/live-in partner. In 16% of cases, condoms were not used because their partner refused. When regular non-paying partner objected to use condom against her wish, refusal of sex happens only in 7% cases, which is very low compared to occasional/regular clients.

In the current study, none of the FSWs had sex with occasional non-paying partners in the last few years (2 to 3 years). Policemen and pimps often used their services but usually also paid for them accordingly.

DISCUSSION

The prevalence of HIV infection in this study population was 7.6% which is higher than the national and state prevalence rate. Most FSWs in this study had their first sexual debut at a very young age, and the majority were illiterate, meaning they had few other options to support themselves. Similar observations are seen in many previous studies among FSW (Dandona et al., 2006, Hemalatha et al., 2011). Most were in the sex trade for economic reasons, to support their families and children financially. However, a fair share had also been forced into sex work from a young age, and some stayed due to debts.

Even though the cumulative knowledge among FSWs in this area appears to be satisfactory, there were knowledge gaps about HIV transmission including breastfeeding as a mode of transmission, sharing meals etc. which may affect social interactions negatively. This may also create uncertainty regarding the perceived risk of HIV among their children, which could influence risk/protective behaviours. On the positive side, 100% had used a condom during their last intercourse with a paying customer and condom use was very high both with regular and non-regular clients. Most of the women felt they had the decision-making power to suggest and decide about condoms.

The almost same pattern was noted by the 'Integrated Behavioural and Biological Assessment' (IBBA) survey conducted among FSW in Maharashtra. It reports that 97 % and 94% brothel-based FSWs used a condom every time with occasional and regular clients respectively in Mumbai and 100% used condom during the last sexual act with these two client categories (ICMR and FHI 360, 2012).

However, in the study, 86% of respondents used more than one condom at the same time, thinking that it will protect them from a possible tear in condoms. In fact, this practice increases the risk of sexually transmitted infections including HIV. Peers and outreach workers

should address this issue by imparting correct knowledge and cultivating a correct practice among them. NACO also envisages targeted interventions among the high-risk populations that include behaviour change, health care, treatment of sexually-transmitted diseases, provision of condoms, and creating an enabling environment for behaviour change to reduce the incidence of HIV.

The study also found that FSWs tends to engage in risky sexual practices with their husbands/lovers or boyfriends. Most of them did not use a condom with such non-paying regular partners thinking that it was not necessary, and also because some partners refused to use condoms and the women had a much lower decision-making power in intimate relationships. A study by Hemalatha et al., (2011) also yielded similar results. According to their study, the principle reason could be that it may signal mistrust in the relationship between FSWs and the non-commercial partner. This is particularly serious given that, as many of these regular male partners also have other partners (36% of FSW's were fully aware, and 14% did not know if their husband/boyfriend/lover had other partners).

The 4th phase of the National Aids Control Program (NACP) is currently being implemented across India, but there is a need to focus on certain aspects. There needs to be concrete and creative efforts to bring regular non-paying partners for HIV screening. Creating positive incentives for couple testing, user-friendly opening hours, mobile testing units that are male friendly are few strategies which can be introduced. The FSWs should be educated and empowered to bring their husbands for HIV screening.

Keeping the perspective of poverty and the high risk in some contexts of being lured and forced into sex work, targeted interventions to educate and support young girls who are at risk of being recruited or forced into sex work is vital. The support mechanism should be social, financial as well as psychological to empower vulnerable young women to stay in school and to meet positive role models. Attempts are also needed to educate young girls in their early teens about HIV prevention programmes, universal sex education etc.

Limitations

The study was conducted in an already among sensitised population within an NGO appears to be a limitation (selection bias). Even then it throws light into many disturbing realities. The sample size was also not so large.

Conclusion

Condom usage, decision-making skills and condom negotiation skills with the regular and one-time client is excellent among the study population which is indeed a good sign. However, special efforts should be made to improve condom usage and decision-making skills in sexual encounters with regular non-paying partners including husbands/lovers. The NGO's working for FSW's should create awareness about the importance of using condoms for every penetrative sexual act irrespective of the type of sexual partners. There is need to undertake special efforts by identifying and involving outreach workers' or peers in reaching out to this key population and organize preventive interventions along with rehabilitation by providing them meaningful employment. These women can be motivated and recruited as peer educators for the FSW community. Thus it gives them employment and all the more increases their knowledge base.

Conflicts of Interests

The authors have not declared any conflict of interests.

REFERENCES

Adhikary R, Gautam A, Lenka SR, Goswami P, Ramakrishnan L, George B, Paranjape RR (2012). Decline in unprotected sex & sexually transmitted infections (STIs) among female sex workers from repeated behavioural & biological surveys in three southern States of India. Ind. J. Med. Res. 136(7): 5.

Dandona R, Dandona L, Kumar GA, Gutierrez JP, McPherson S, Samuels F, Bertozzi SM (2006). Demography and sex work characteristics of female sex workers in India. BMC Int. Health Human Rights 6(1):1.

Dasra (2013). Zero Traffick-A brief overview of sex trafficking in India.

Hemalatha R, Kumar RH, Venkaiah K, Srinivasan K, Brahmam GNV (2011). Prevalence of & knowledge, attitude & practices towards HIV & sexually transmitted infections (STIs) among female sex workers (FSWs) in Andhra Pradesh. Ind. J. Med. Res. 134(4): 470.

Indian Council of Medical Research and FHI 360 (2012). State Summary Report –Maharashtra, Integrated Behavioural and Biological Assessment (IBBA), Round 1 (2005-2007) and Round 2 (2009-2010). New Delhi.

National AIDS Control Organization (2015). National AIDS Control Organization-Annual Report. Department of AIDS Control Society, Ministry of Health and Family Welfare.

National AIDS Control Organization (2016a). HIV sentinel surveillance. Ministry of Health and Family Welfare.

National AIDS Control Organization (NACO) (2016b). National Integrated Biological and Behavioural Surveillance (IBBS) 2014-15.

National AIDS Control Organization, National Institute of Medical Statistics and Indian Council of Medical Research (2015). India HIV Estimations 2015.

World Health Organization (WHO) (2015). Country Fact Sheet- India.

academicJournals

Vol. 9(1), pp. 8-16, January 2017
DOI: 10.5897/JAHR2016.0399
Article Number: 4ABC56262101
ISSN 2141-2359

http://www.academicjournals.org/JAHR

Journal of AIDS and HIV Research

Full Length Research Paper

Evaluation of the frequency of use of herbal drugs with concomitant administration of highly active antiretroviral therapy and its effect on medication adherence in two health care facilities in south western Nigeria

Ilomuanya Margaret O[1], Okubanjo Omotunde O[1]*, Azubuike Chukwuemeka[1], Oguntibeju Adeyemi[2], Ajiboye Dolapo[1] and Maduka Chima[3]

[1]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, College of Medicine Campus, P.M.B. 12003, Surulere, University of Lagos, Lagos State, Nigeria.
[2]Olusola Ojo Primary Health Center, Resthouse Street, Ojo Local Government Area, Ojo Lagos, Lagos State, Nigeria.
[3]Faculty of Pharmacy, Igbinedion University Okada, Okada PMB 0006 Benin City, Edo State, Nigeria.

Received 14 October, 2016; Accepted 28 November, 2016

The aim of this study was to evaluate the prevalence of the concomitant use of herbal medicine and anti-retroviral drugs in people living with HIV/AIDs and to evaluate the reasons given by the patients for concomitant administration of highly active antiretroviral therapy (HAART) with herbal drugs in order to establish a possible link between the use of herbal medicines and adherence. A cross sectional study design was utilized via systematic sampling for recruitment of HIV positive individuals receiving their medications in Amuwo-Odofin and Ojo areas in Lagos, Nigeria. Based on the inclusion criteria, 351 HIV positive patients were recruited into the study from the HIV outpatient clinics of two hospitals and had the questionnaires administered to them. 42.7% of the respondents stated that they use herbal medicines. The association for each of the herbal medicines with side effects experienced with the use of ARVs was statistically significant upon cross-tabulation and was a major predictor of herbal drug use. The prevalence of herbal drug use in patients who were adhering to HAART medication was not significantly different from those who were not adhering to medication ($p = 0.75$ and $\chi^2 = 6.902$). The use or lack of use of herbal medicine is not a determinant for adherence. The most profound reason for herb use was to improve treatment. However, herb/drug interaction studies are imperative to ascertain if interactions occurring are beneficial or harmful. The pharmacist must counsel and re-counsel patients on HAART, not to use herbal products with their antiretroviral medications to avoid drug-herb interactions which could be potentially life threatening.

Key words: Highly active antiretroviral therapy (HAART), herbal drugs, adherence.

INTRODUCTION

World Health Organization (WHO) estimates show that 33.4 million people globally were living with HIV/AIDS and there were 2.0 million AIDS-related deaths in 2015 (WHO, 2015). In sub-Saharan Africa, 22.4 million adults

and children are currently living with HIV/AIDS, representing more than 60% of the global burden of the disease. Nigeria, the most populous country in Africa, is estimated to have about 5 million of the population infected with human immunodeficiency virus (HIV), making it the third largest population in the World infected with the dreadful virus (WHO, 2015).

HIV, caused by the retrovirus is not just a health problem but also a socioeconomic issue as it affects the working population (18-45 years of age) and sexual intercourse mainly is the route of transmission (Wanyenze et al., 2011). Nigerians have a firm belief in the use of herbal remedies for major illnesses (Anabwani and Navario, 2005). HIV infection has no cure medically; hence, this serves as a catalyst to source for cure in herbal remedies (Anabwani and Navario, 2005). Since confirmation of the HIV infection in Nigeria in 1987, after identification of the virus in the 1980's, herbal therapists in Nigeria have been searching for the cure (Abalaka, 2004). This led to many claimed curative medicines or vaccines emanating from Nigeria (Abalaka, 2004). The safety of herbal remedies had been a major concern to health care practitioners especially when the chemical constituents of the product are not known.

According to the World Health Organization, herbal remedies are herbs, herbal materials, herbal preparations and finished herbal products, used to treat a multitude of ailments throughout the world (Amira and Okubadejo, 2007). There are many classes of herbal remedies used for HIV infection based on their chemical constituents such as: alkaloids, carbohydrates, coumarins, flavonoids, lignans, phenolic, proteins, quinones, terpenes and tannins. There are many herbal remedies that are being used in Nigeria for HIV infection. Many of these herbal remedies are used as complementary therapy to HAART; thus, necessitating toxicological studies to be carried out on some herbal products in Nigeria using varying models (Abere and Agoreyo, 2006).

Unlike the assumptions that herbal remedies are harmless because of the natural source, many have been found to be toxic (Chatora, 2003; Cos et al., 2004). Thus, safe herbal remedies are being identified and their use is encouraged, while the use of harmful herbal products is discouraged (Hanapi et al., 2010). Unfortunately, many consumers do not know which herbal remedies are safe, thus the general acceptance or rejection of the herbal products (Hanapi et al., 2010). It was estimated that over 70% of HIV patients taking herbal remedies denied taking them when asked by medical practitioners (Hanapi et al., 2010). This denial by HIV patients may constitute a deterrent to the medical practitioners in early detection of possible negative drug interactions that could occur with orthodox medicines especially HAART. Traditional herbal medicine has become more popular among HIV/AIDS patients as adjuvant therapy to reduce the adverse effects of HAART (Zhang et al., 2011). Regardless of the subsidized and physical availability of the HAART, majority of Africans living with HIV/AIDS resort to adding to their HAART, traditional herbs e.g. bitters and other herbal mixtures because they either lack the financial means to enable them access the drugs or cannot bear the side effects related to these drugs or believe that there is need for an additional therapy that can permanently cure them of the disease. Concomitant uses of HAART with some herbal remedies with high antioxidant content have been reported to be beneficial in the treatment of oxidative stress amongst some HIV infected individuals (Sharma, 2014). Negative drug interactions between some herbs like garlic and St John's Wort with HAART have been established (Hsiao et al., 2003; Zhang et al., 2011). African potato *Hypoxis* spp. and *Sutherlandia frutescens* have caused potential harmful interactions with anti-retroviral drugs (Blench, 2006).

The study therefore aims at studying the prevalence of the concomitant use of these herbal mixtures like bitters containing different herbs, Ginger, Moringa, locally brewed concoctions generally termed "*agbo*" with HAART and the effect it has on adherence and also evaluate the reasons for the concomitant administration of HAART with these herbal drugs in western Nigeria.

METHODOLOGY

Study site

Data collection was done between November 2015 and January 2016 at two ART clinic sites in Lagos State being Holy Family Catholic Hospital Festac town Amuwo Odofin Local government area and the Olusola Ojo Primary Health Center, Ojo Local Government Area both in Lagos Western Nigeria. The former is a faith-based hospital in an urban area; the latter center is situated in a semi-urban area and is a government hospital. Both centers are well equipped with adequate staff to run the following HIV related programmes; Prevention of mother to child transmission (PMTCT), HIV testing and counselling and HIV care via provision of HAART.

Study population and study design

Only one treatment subgroup was utilized, that is, only patients on HAART were interviewed. A cross sectional study design was utilized via systematic sampling for recruitment of HIV positive individuals. The inclusion criteria was being a HIV positive adult between 18 and 60 years and being on HAART, receiving these

*Corresponding author. E-mail: omotundeokubanjo@yahoo.co.uk; mokubanjo@unilag.edu.ng. Tel: +234-8037147599.

medications at one of the study centers used for this study. During the clinic days, the staff attending to the patients asked every second male and female if they would be interested in participating in this research, where a positive response was obtained and the patient met the inclusion criteria he was directed to a research assistant who then furnished the patient with more information and the study consent. An interviewer questionnaire was used and prevalence of concomitant administration of HAART, with herbal drugs determined.

Sample size calculation was based on the assumption that 75% of the Nigerian population utilizes herbal drugs in one form or the other (Bamidele et al., 2009; Abere and Agoreyo 2006). The level of significance utilized for this study was 0.05 and a power of 0.75 was obtained based on the assumption of the number of Nigerians using herbal medicines. Utilizing sample size calculator NSS version 12.0 (2013), Australian Bureau of Statistics, a sample size of 351 was obtained.

HIV positive patients receiving HAART were treated according to the National guidelines of the Federal Ministry of Health and the National Agency for the control of AIDS in Nigeria. Fixed dose combinations (FDC) for First line treatment comprised of Lamivudine/Zidovudine and Nevirapine (FDC) or Lamivudine/Tenofovir and Efavirenz (FDC). FDC for second line treatment comprised of Atazanavir- Ritonavir/Lamivudine/Tenofovir or Lopinavir-Ritonavir (Alluvia®)/Lamivudine/Tenofovir. These were the combinations utilized by patients in this study.

Data collection instrumentation

The material/instrument used was the semi-structured questionnaire combining closed and open-end questions. The questionnaire contained two sections; personal information and the other section contained questions directed at determining the prevalence of concomitant administration of HAART and herbal drugs/traditional and complimentary medicines. The questionnaires were first pretested using 10 HIV positive patients not enrolled in the study, the interview lasted an average of 17 min. With the aid of an interpreter, verified by another translator, individuals who do not speak English were attended to in the language they felt most comfortable with. At the start of the study, a randomized sample of 20 respondents underwent a test – retest procedure to assess the reliability of questionnaire responses. An 8-day time interval was given for the re-test to ascertain the reliability of the questionnaires.

Data analysis

Statistical analysis was carried out using the Chi-square tool of SPSS version 21.0 with a $p < 0.05$ level of significance.

Study approval and ethics consideration

The Lagos University Teaching Hospital Research Ethics Committee of the College of Medicine University of Lagos provided ethical approval for the study (CM/HREC/02/16/002). Approval was also obtained from the medical directors of the institutions utilized as HIV/AIDS treatment sites. Each participant was duly informed of the study and asked to sign consent forms. Participant's identities were kept anonymous after identification numbers were assigned to each participant.

RESULTS AND DISCUSSION

Based on the inclusion criteria for the study, 351 HIV positive patients were recruited into the study. Within the study sample, 52.7% of the respondents stated that they do not use herbal medicines, while 42.7% stated that they use herbal medicines despite being asked not to do so prior to commencing antiretroviral treatment. Traditional extract known in Yoruba language as *agbo* was the most commonly used herbal medicine. The frequency ranking for the other herbal medicines was bitter leaf>holy water>ginger> Moringa infusion>bitters as shown in Figure 1. 44.1% of the respondents stated that their reason for using herbal medicines was to improve treatment while 12.5% of the respondents stated that they were given these herbal mixtures by family and friends to take because of the chronic nature of the disease they were battling with (Figure 2). The association between socio-demographic characteristics and the use of herbal medicine was not statistically significant (Table 1). Table 2 shows a statistically significant association between the knowledge of the use of herbal medicines and the use of herbal medicines. Cross-tabulation of each of the side effects experienced by respondents as a result of the use of their ARVs and use of herbal medicines showed that there was no statistically significant relationship amongst those that experienced bad dreams, weight loss and vomiting and the use of herbal medicines.

The use of herbal remedies has been extensively studied in Nigeria among varying demographics; pediatrics, diabetics, sickle-cell anemia patients and terminally ill patients suffering from malignancies as well as in the general population (Oreagba et al., 2011). Herbal medicine use varies form 27.95% to as high as 72.43% in some demographics studied (Oreagba et al., 2011). There has been paucity of data documenting herbal drug use among retroviral positive patients especially because these groups of patients are usually asked not to co-administer these medicines with their antiretroviral drugs. The prevalence of herbal drug use in this study was 47.3% without any significant difference in the pattern of use between males and females $p = 0.88$ and $\chi^2 = 2.902$ (Table 1).

Out of 351 HIV-infected persons recruited into the study, there were more females (72.4%) than males (27.6%) and more employed people (69.2%) than unemployed people (30.8%). Majority of the respondents (68.9%) were within the age group of 25-45 years. Overall, most of the participants had attained at least secondary level of education while a small proportion of respondents (5.1%) had no formal education. There was no statistically significant association between socio-demographic characteristics (gender, age, employment status and level of education) and the use of herbs. Similar results were obtained where it was reported that having a rural dwelling, female gender, older age, a lack of formal education, not being married, having employment and haven been HIV positive for less than

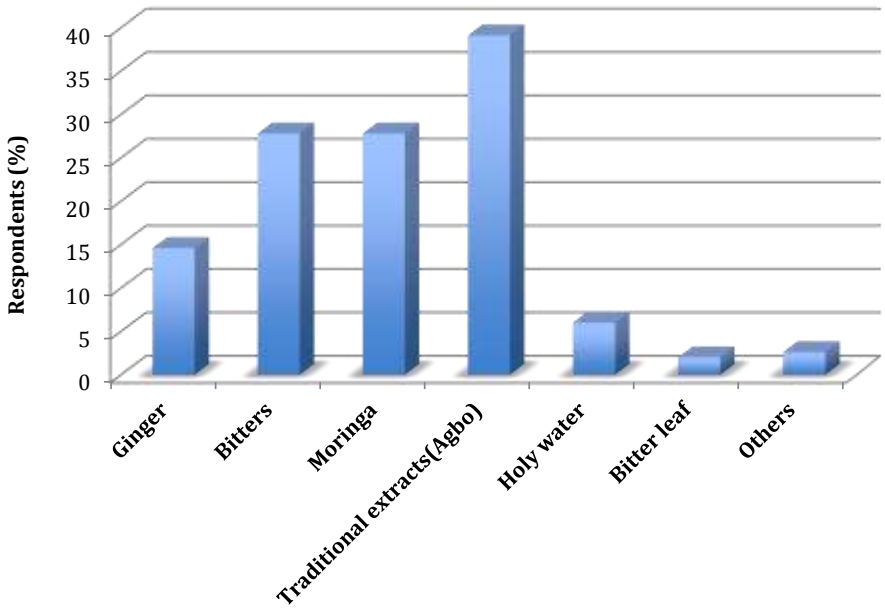

Figure 1. Frequency distribution of herbal medicine utilized by the population examined.

5 years were all predictors of traditional medicine use amongst people living with AIDS (Oreagba et al., 2011; Hughes et al., 2012).

Traditional herbal medicine was not commonly used by the study respondents, with 185 (52.7%) of the respondents claim that they do not use herbal medicines. This response may be premeditated and could be due to instruction from the pharmacist that they will be denied access to HAART if they did use them concurrently with herbal products. This instruction given by the pharmacist is as a result of known interaction between herbal medicines and antiretrovirals (Hanapi et al., 2010). The findings from this study shows that a greater proportion of the respondents do not use complementary herbal medicines with ARVs. This observation is contrary to the earlier report of Duggan et al. (2001) that reported 67% of a group of examined students concurrently used herbal medicine with antiretrovirals. The low proportion of respondents that use herbal medicines obtained in this study may be due to the continuous adherence to the counseling offered to patients to avoid taking herbal medicines with ARVs because of potential interaction and adverse effects. The association between knowledge of the use of herbal medicine and the actual use of herbal medicine was significant with 51.7% of the respondents who used herbal medicines reporting they had been advised not to do so by the pharmacist as shown in Table 2. This could also be due to the influence of family, friends and prevalence of advertisements in the media that herbal remedies have potentials in combating all forms of ailments.

However, among those who reported that they use herbal medicine, traditional extracts (agbo) were the most commonly used herbal medicine, used by 109 (31.1%) of the respondents. This finding compares favorably with earlier studies (Oreagba et al., 2011; Hughes et al., 2012). This is probably due to the belief of these individuals that the different constituents in the 'agbo' are able to bring them speedy healing.

Majority of the respondents (44.1%) stated that their reason for using herbal medicines was to improve treatment (Figure 2). Also, majority (66.1%) of the respondents stated that a pharmacist/pharmacy attendant/counselor spoke to them about the use of herbal drugs.

As regards side effects, majority (68.9%) of the respondents stated that they do not experience side effects from the ARVs they were using. However, for those that stated that they experienced side effects, majority (14%) stated that they experience side effects other than bad dreams, anaemia, blurred vision, weight loss, weight gain and vomiting. Some side effects characteristic of ARVs includes vomiting (Tenofovir, Zidovudine, Efavirenz), anaemia (Zidovudine), rashes (Nevirapine), diarrhoea (Abacavir), bad dreams (Efavirenz). These side effects may not necessarily be as a result of the herbal medicines used. On the other hand, some herbal medicines may cause side effects such as nausea and vomiting (bitters), skin irritation, heartburn (ginger), paralysis (root extract of *Moringa Oleifera*) (Sharma 2011 et al., Amzat and Abdullahi 2008). There was a statistically significant association between side

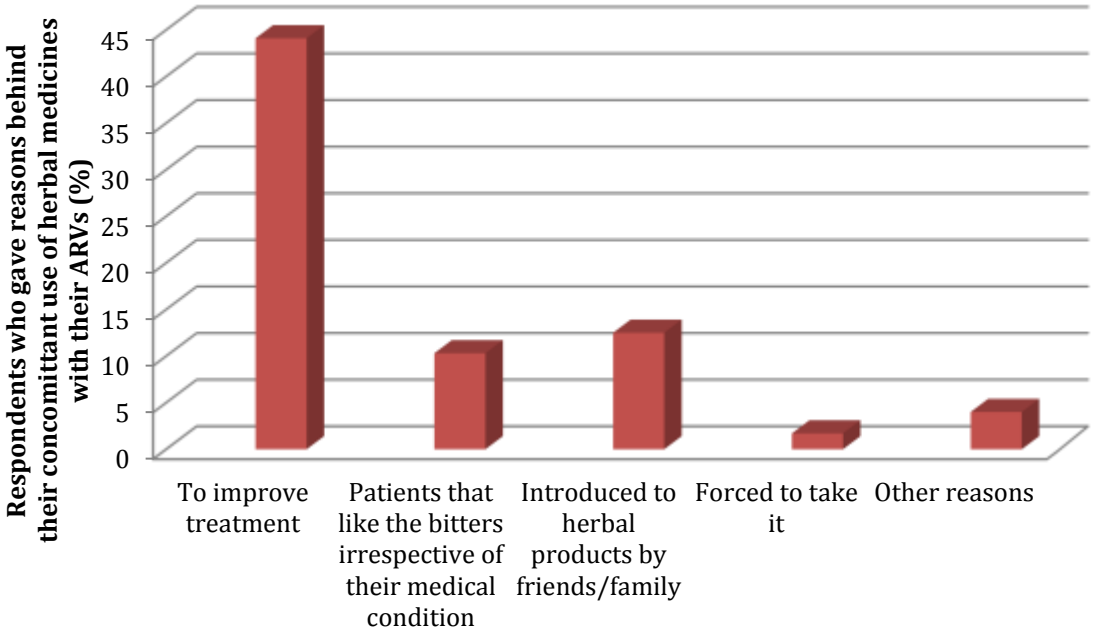

Figure 2. Reasons given by respondents for concomitant use of antiretroviral treatment with herbal medicines.

Table 1. Association between socio-demographic characteristics and use of herbs.

Variable	Use of herbs			
	Yes	No	Total	
Gender				
Female	113 (44.5%)	141 (55.5%)	254	χ^2 = 2.902
Male	53 (54.6%)	44 (45.4%)	97	P = 0.88
Total	166 (47.3%)	185 (52.7%)	351	
Employment Status				
Employed	118 (48.6%)	125 (51.4%)	243	χ^2 = 0.508
Unemployed	48 (44.4%)	60 (55.5%)	108	P = 0.476
Total	166 (47.3%)	185 (52.7%)	351	
Age				
15-24 years	18 (51.4%)	17 (48.6%)	35	χ^2 =4.418
25-45 years	121 (50.0%)	121 (50.0%)	242	P = 0.110
46-60 years	27 (36.5%)	47 (63.5)	74	
Total	166 (47.38%)	185 (52.7%)	351	
Level of education				
Primary	29 (50.9%)	28 (49.1)	57	χ^2 = 0.809
Secondary	84 (47.2)	94 (52.8)	178	P = 0.847
University	46 (46.9)	52 (53.1)	98	
No formal education	7 (38.9)	11 (61.1)	18	
Total	166 (47.3)	185 (52.7)	351	

No significant association between socio-demographics of respondents and their herb usage.

Table 2. Association between knowledge of the use of herbal medicine and the use of herbal medicine.

Knowledge of the use of herbal medicine			Use of herbal medicine		Total
			Yes	No	
	YES	Count	120	112	232
		% within	51.7%	48.3%	100.0%
	NO	Count	46	73	119
		% within	38.7%	61.3%	100.0%
Total		Count	166	185	351
		% within	47.3%	52.7%	100.0%

	*Chi-square tests				
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-square	5.389[a]	1	0.020	-	-
Likelihood ratio	5.427	1	0.020	-	-
No. of valid cases	351	-	-	-	-

*Chi square test indicates significant association between knowledge of the use (whether respondents had been informed about not using HAART with herbal medicine) and the actual use of herbal medicine.

effects and the use of herbal extracts. This can be explained by the fact that traditional extracts contain a variety of active constituents and so the actual constituent causing the side effect may be unknown.

Adherence plays a vital role in the treatment outcome of retroviral positive patients as patients that adhere to their medications are likely to retain their CD4 at higher than 200 cells/mm^3 and enjoy a good quality of life as shown in Table 3. The prevalence of herbal drug use in patients who were adhering to HAART medication was not significantly different from those who were not adhering to medication, $p = 0.75$ and $\chi^2 = 6.902$. The use or lack of use of herbal medicine was therefore not a determinant for adherence. The respondents were acutely aware of the need for them to adhere to HAART, as such; only 4.8% of the respondents who stated that they had missed more than one dose of their ARVs in the past month stated they forgot to take their medications. The level of adherence among the population studied was very high with 90.4% stating that they had not missed a dose in 3 months, this was associated with the caregivers and support group's periodic counseling on the need for drug adherence to prevent patients from having opportunistic infections like tuberculosis.

Most of the respondents (4.8%) who stated that they had missed more than one dose of their ARVs in the past month stated that the reason was that they ran out of pills. This may be untrue, as the pills are given to patients for free and can be explained by the patients resorting to using herbal medicines. Similar studies carried out by Peltzer et al. (2008) and Banda et al. (2007) have shown that patients using herbal treatments in conjunction with ART are more likely to take gaps in treatment or reduce their level of adherence. Also, majority of the respondents (66.1%) stated that they are not part of a support group. Being part of a support group has been shown to encourage adherence to antiretroviral therapy. 69.5% respondents with CD4 count > 200 cells/mm^3 were more in this study with majority (44.3%) claiming that they do not use herbal drugs while majority of the respondents with CD4 count less than 200 cells/mm^3 (44.5%) state that they use herbal drugs (Table 3). This finding is similar to that of a 2008−2011 study in Kampala, Uganda where Wayneze et al. (2011), found that patients who had reported receiving treatment from traditional healers or other informal sources had lower CD4 counts at treatment initiation. However, the association between CD4 count and the use of herbal drugs was not statistically significant.

A greater percentage of respondents (60.4%) with poor quality of life use herbal drugs, as compared to those with good and very good quality of life, respectively (Table 3). This could be due to the fact that they felt the use of herbal drugs complemented the ARVs thus making it more beneficial to their wellbeing. The association between use of herbal drugs and overall quality of life was statistically significant with $p = 0.058$ and $\chi^2 = 0.902$.

According to estimates by World Health Organisation (WHO) and Joint United Nations Programme on HIV and AIDS (UNAIDS), 36.9 million people were living with HIV globally at the end of 2011 (WHO 2011). That same year, some 2 million people became newly infected, and 1.2 million died of AIDS related causes. With more than 34 million infected individuals, the prevalence of Human

Table 3. Evaluation of the interaction of variables influencing herbal drug use and its implication on adherence.

Variable	*Percentage (%)
Do you use herbal drugs?	
Yes	47.3
No	52.7
How often do you use herbal drugs?	
Never	52.4
Daily	4.6
Weekly	16.0
Monthly	15.1
One a year	8.5
Cannot remember	3.4
Which herbal medicines do you use?	
Ginger	9.7
Bitters	18.8
Traditional extracts (agbo)	15.4
Holy water/spiritual healing/prayers	31.1
Bitter-leaf	4.0
Others	
Why do you use herbal medicines	
To improve treatment	33.6
Because I like it	10.5
It makes me feel better	10.3
I was forced to take it	1.7
It was introduced to me by friend/family	12.5
others	4.0
Did a pharmacist/pharmacy attendant/counsellor talk to you about the use of herbal medicines?	
Yes	66.1
No	33.9
Do you experience side effects from the antiretrovirals?	
Yes	30.8
No	68.9
New comer	0.3
Side effects from antiretrovirals experienced	
Bad dream	6.0
Blurred vision	5.7
Anaemia	8.5
Weight gain	1.7
Weight loss	4.3
Vomiting	6.3
Others	14.0
Reason for missing more than one dose of ARV in the past month	
Away from home	4.3
Wanted to avoid side effects	2.3
Felt sick/ill	1.4

Table 3 cont'd

Felt good	**0.0**
Had too many pills to take	0.9
Busy with other things	2.6
Ran out of pills	4.8
Fell asleep/slept through dose time	2.3
Had problems taking pills at specified times	0.6
Simply forgot	4.3
Felt depressed/overwhelmed	2.6
Felt like the drug was toxic/harmful	0.0
Had a change in daily routine	0.9
Did not want others to notice	1.4
CD4 count	
>200	69.5
<200	28.8
Newly screened	1.7
Are you part of a support group?	
Yes	32.8
No	66.1
HIV staging	
STAGE 1	46.7
STAGE 2	32.8
STAGE 3	16.5
STAGE 4	4.0
Overall Quality of Life	
Very poor	1.1
Poor	13.7
Good	73.5
Very good	11.7

*% Values signify frequency of occurrence of variables as indicated by respondents.

Immunodeficiency Virus (HIV) infection remains a perturbing pandemic that has been projected to be one of the most serious significant public health concerns. Nonetheless, the introduction of HAART has significantly reduced AIDS related morbidity and mortality rate. Although, the quality of life of those infected have been improved, patients continue to experience physical and emotional discomforts due to the infection and/co-infection and related treatment and this could be one of the reasons they resort to using herbal medicines (Oreagba et al., 2011). The use of herbal medicines is viewed to be without risk by patients due to their ethnobotanical origins. It is for this reason that respondents still utilize these herbal products even when advised not to do so by their health care givers. Drug-herb interactions occurring from this concomitant administration may be under reported, as patients do not readily disclose to physicians or pharmacist the complimentary/ alternative therapies they are using. The proliferation of registered herbal products has generated a lot of public awareness and has brought about the need for regulation of the doses of these herbal remedies to prevent herbal medicine toxicity. Patients suffering from chronic illnesses which have no cure are especially attracted to herbal medicines; hence, the formulation of herbal medicines into metered dosage forms can be beneficial in terms of detecting the actual or approximate amounts of active ingredients of herbal medicines that may be toxic; thus, creating a safety profile for them. Studies have shown the presence of heavy metals in the traditionally prepared herbal medicines locally called *agbo,* which may subsequently have adverse interaction

with HAART and affect patient overall well being, the very parameter which was the main reason why the 44.1% respondents opted to take the herbal medicines.

Conclusion

The use or lack of use of herbal medicine was not a determinant for adherence. The respondents who used herbal medicines concomitantly with HAART did so because they believed that it improved their treatment. The authors recommend herb/drug interaction studies in order to ascertain if interactions that occur between HAART and herbs are beneficial or harmful. Since this information is not yet available, the pharmacist must counsel and re-counsel patients on HAART not to use herbal products concomitantly with their antiretroviral medications to avoid drug-herb interactions which could be potentially life threatening.

Conflict of interest

The authors have not declared any conflict of interest.

ACKNOWLEDGEMENT

This research work was made possible by the Central Research Committee of the University of Lagos Mini Grant CRC NO. 2016/08.

REFERENCES

Abalaka JO (2004). Attempts to cure and prevent HIV/AIDS in central Nigeria between 1997 and 2002: opening a way to a vaccine-based solution to the problem? Vaccine 22:3819-3828.

Abere TA, Agoreyo FO (2006). Antimicrobial and toxicological evaluation of the leaves of Baissea axillaries Hua used in the management of HIV/AIDS. BMC Complement Altern. Med. 21:(6):22.

Amira OC, Okubadejo NU (2007). Frequency of Complementary and Alternative Medicine Utilization in Hypertensive Patients Attending an Urban Tertiary Care Centre in Nigeria. BMC Complement. Altern. Med. 7(30):1-5.

Amzat J, Abdullahi AA (2008). Role of Traditional Healers in the Fight against HIV/AIDS. EthnoMed. 2(2):153-159.

Anabwani G, Navario P (2005). Nutrition and HIV/AIDS in sub-Saharan Africa: an overview. Nutrition 21:96-99.

Australian bureau of Statistics, National Statistics service (NSS). Available at: http://www.nss.gov.au/nss/home.nsf/pages/Sample+size+calculator

Bamidele J, Adebimpe O, Oladele E (2009). Knowledge, attitude and use of alternative medical therapy amongst urban residents of Osun State South-western Nigeria. Afr. J. Tradit. Complement. Altern. Med. 6(3):281-288.

Banda Y, Chapman V, Goldenberg RL, Stringer JS, Culhane JF, Sinkala M, Vermund SH, Chi BH (2007). Use of Traditional Medicine among Pregnant Women in Lusaka, Zambia. J. Altern. Complement. Med. 13(1):123-127.

Blench R, Dendo M (2006). Fulfulde names for plants and trees in Nigeria Cameroun, Chad and Niger, Cambridge. (2006). Available at: http://www.rogerblench.info/Ethnosciencedata/FulfuldePlantnames.pdf

Chatora R (2003). An overview of the traditional medicine situation in the African region. Afr. Health Monit. 4(1):4-7.

Cos P, Maes L, Berghe D, Hermans N, Pieters L, Vlietinck A (2004). Plant substances as anti-HIV agents selected according to their putative mechanism of action. J. Nat. Prod. 167:284-293.

Duggan J, Peterson WS, Schutz M, Khuder S, Charkraborty J (2001). Use of complementary and alternative therapies in HIV-infected patients. AIDS Patient Care STDS (3):159-167.

Hanapi NA, Azizi J, Ismail S, Mansor SM (2010). Evaluation of selected Malaysian medicinal plants on phase I drug metabolizing enzymes, CYP2C9, CYP2D6 and CYP3A4 in vitro. Int. J. Pharmacol. 6:494-499.

Hsiao AF, Wong MD, Kanouse DE (2003). Complementary and alternative medicine use and substitution for conventional therapy by HIV-infected patients. J. Acquir. Immune Defic. Syndr. 33(2):157-65.

Hughes GD, Puoane TR, Clark BL, Wondwossen TL, Johnson Q, Folk W (2012). Prevalence and Predictors of TM Utilisation among Persons Living With AIDS (PLWA) on Antiretroviral (ARV) and Prophylaxis Treatment in both Rural and Urban Areas in South Africa. Afr. J. Tradit. Complement. Altern. Med. 9(4):470-484.

Oreagba IA, Oshikoya KA, Amachree M (2011). Herbal Medicine use among urban residents in Lagos, Nigeria. BMC Complement. Altern. Med. 11:117-119.

Peltzer K, Phaswana-Mafuya N (2008). The Symptom Experience of People Living with HIV and AIDS in the Eastern Cape, South Africa. BMC Health Serv. Res. 8:271-273.

Sharma B (2011). The antiHIV-1 drugs toxicity and management strategies. Neurobehav. HIV Med. 3:1-14.

Sharma B (2014). Oxidative stress in HIV patients receiving antiretroviral therapy. Curr. HIV Res. 12(1):13-21.

Wanyenze RK, Kamya MR, Fatch R, Mayanja-Kizza H, Baveewo S, Sawires S, Bangsberg DR, Coates T, Hahn JA (2011). Missed opportunities for HIV testing and late-stage diagnosis among HIV-infected patients in Uganda. 1:1128-1135. PLoS One 6(7):e21794.

World Health Organization (WHO) (2015). Global HIV/AIDS Overview Available at: https://www.aids.gov/federal-resources/around-the-world/global-aids-overview/

World Health Organization (WHO) (2011). Programmes and projects. Traditional medicine. Available at: http://www.who.int/medicines/areas/traditional/en/index.html

Zhang FJ, Dou ZH, Ma Y (2011). Effect of earlier initiation of antiretroviral treatment and increased treatment coverage on HIV-related mortality in China: a national observational cohort study. Lancet Infect. Dis. 11:516-524.

academicJournals

Vol. 9(1), pp. 17-30, January 2017
DOI: 10.5897/JAHR2016.0406
Article Number: 24E08CE62105
ISSN 2141-2359

http://www.academicjournals.org/JAHR

Journal of AIDS and HIV Research

Full Length Research Paper

Evaluating an enhanced adherence intervention among HIV positive adolescents failing atazanavir/ritonavir-based second line antiretroviral treatment at a public health clinic

Tariro Dianah Chawana[1]*, David Katzenstein[2], Kusum Nathoo[3], Bernard Ngara[4] and Charles Fungai Brian Nhachi[1]

[1]Department of Clinical Pharmacology, University of Zimbabwe, Harare 00263, Zimbabwe
[2]Department of Medicine, Division of Infectious Diseases, Stanford University, California.
[3]Department of Paediatrics, University of Zimbabwe, Harare 00263, Zimbabwe.
[4]Department of Community Medicine, University of Zimbabwe, Harare 00263, Zimbabwe.

Received 17 November, 2016; Accepted 7 December, 2016

Sustaining virological suppression among HIV-infected adolescents is challenging. We evaluated a home-based adherence intervention and characterized self-reported adherence, virological response and drug resistance among adolescents failing atazanavir/ritonavir (ATV/r)-based 2nd line treatment. Methods: HIV-positive adolescents (10-18 years) on ATV/r-based 2nd line treatment with virological failure (viral load (VL) ≥1 000 copies/ml) were randomized to either standard care (SC) or SC with addition of modified directly administered antiretroviral therapy (mDAART) for 90 days. VL was measured and questionnaires were administered at study entry and at 3 months. Genotyping was done for participants with continued failure. Primary outcome was suppression to VL < 1 000 copies/ml. Results: Fifty adolescents aged 10-18 years on 2nd line treatment for >180 days were enrolled, 23(46%) were randomized to mDAART and 27(54%) to SC. Fifty-four percent were female; mean age was 15.8 years; mean baseline VL was 4.8(log_{10}) copies/ml; 40% reported adherence <80% in previous 1 month at baseline; 40% suppressed (VL <1 000 copies/ml) after follow-up. mDAART resulted in significantly increased self-reported adherence (RR= 0.1; 95% CI=0.02-0.8, p=0.023); closely following dosing schedule (RR= 4.8; 95% CI=1.6-13.8, p=0.004); VL decrease (p=0.031) and modest increase in virological suppression to <1 000 copies/ml (p=0.105). Genotyping in 28/30 participants with continued virological failure demonstrated high level atazanavir resistance (I50L, N88S and I84V) in 6(21%); 3(11%) of whom also had high level resistance to lopinavir and darunavir (V32I, I50L, I54V, 147V and V82A). Discussion: The mDAART intervention modestly improved virological suppression among adolescents with ATV/r-based 2nd line treatment failure, significantly increased self-reported adherence and decreased viral load. High level ATV/r resistance was demonstrated. Conclusion: Targeting mDAART to adolescents who are virologically failing PI-based 2nd line treatment decreases viral load and increases self-reported adherence. Early drug-resistance testing could reduce morbidity and mortality.

Key words: Adolescents, HIV, second-line treatment failure, adherence, resistance.

INTRODUCTION

Global scale-up of antiretroviral therapy (ART) has significantly reduced HIV-related morbidity and mortality. However, sub-Saharan Africa (SSA) continues to bear the highest burden of HIV infection in the world, accounting for about 90% of all HIV infections (World Health Organisation, 2014). About 2.1 million adolescents (10-19 years of age) in 2012 were living with HIV globally (Lowenthal et al., 2014; WHO, UNAIDS, UNICEF, 2011). Over 10,000 HIV-infected adolescents were registered in HIV-care services in 2008 in Zimbabwe (Ferrand et al., 2010). Adolescents present important challenges to access, adherence and retention in care. Literature reports that 20 to 50% of HIV-infected adolescents on 2nd line are failing treatment (Nglazi et al., 2012; Suaysod et al., 2015). Adolescents who fail boosted protease inhibitor (PI)-based 2nd line regimens in resource-limited settings (RLS) have limited treatment options for salvage therapy, poor treatment outcomes, pose a risk of transmitting drug resistant virus and are at higher risk of subsequent treatment failure (Gupta et al., 2012; Hosseinipour et al., 2013).

Virological failure in adolescents is thought to be a result of poor adherence (Garone et al., 2014; Lessells et al., 2013; Levison et al., 2012). Paterson reported that >95% adherence is required for viral suppression on non-nucleotide reverse transcriptase inhibitors (NNRTIs) and boosted bPIs (Paterson et al., 2000). However, Kobin and Shutter later argued that for patients on boosted PIs, adherence rates of at least 80% are required for a minimum of 80% of patients to achieve viral suppression and that mean adherence required for viral suppression is 75% (Roux et al., 2011; Shuter et al., 2007; Shuter, 2008). Boosted PIs are therefore more 'forgiving' than NNRTIs.

Drug resistance could also cause 2nd line treatment failure. Poor adherence selects drug resistance mutations due to on-going viral replication at sub-inhibitory PI concentrations (Nachega et al., 2009). However, boosted PIs have high genetic barrier to resistance, typically requiring multiple mutations, rather than single point mutations, for clinically significant drug resistance (Rhee et al., 2015; Tang and Shafer, 2012). Many studies of boosted PIs have noted the absence PI resistance in patients failing PI-based 2nd line treatment (Garone et al., 2014; Levison et al., 2012).

The reasons why a high proportion of adolescents may fail boosted PI based 2nd line treatment include poor adherence and evolution of drug resistance. If sub-optimal adherence is the reason, intensive adherence interventions should result in viral suppression. If drug resistance is the cause of treatment failure, then HIV drug resistance testing and the use of 3rd line drugs, such as darunavir/ritonavir and raltegravir, amongst others, should be prioritised (Panel on antiretroviral guidelines for adults and adolescents and Department of Health and Human Services 2012; Panel on Antiretroviral Therapy and Medical Management of HIV Infected Children 2012). Identifying and addressing the cause of treatment failure in adolescents on boosted PI-based regimens will reduce the need for largely unavailable and expensive 3rd line treatment.

This study sought to determine and quantify the causes of virological non-suppression, and determine if a home-based adherence intervention and standard care improved virological suppression in HIV-infected adolescents who are virologically failing atazanavir/ritonavir (ATV/r)-based 2nd line treatment compared to standard care alone.

METHODS

Study design

A randomised, controlled trial (RCT) comparing modified directly administered antiretroviral therapy (mDAART) + standard care (SC) versus SC + self-administered treatment (SAT) for 90 days. Data was collected between January 2015 and May 2016. Eligible participants were included if they: were HIV positive with a documented result; were aged between 10 and 18 years; were on ATV/r-based 2nd line treatment for ≥6 complete consecutive months; had virological treatment failure (viral load ≥1 000 copies/ml); knew their HIV status; provided informed consent and assent; were registered at Harare hospital paediatric opportunistic infections clinic and stayed within Harare hospital catchment area. Adolescents were consecutively screened for eligibility using a questionnaire and viral load measurement. The screening viral load was also used as baseline for enrolled participants. Participants were excluded if they were on anti-TB treatment; did not want to be followed-up at home; had viral load <1 000 copies/ml within the previous 2 months or were on ATV/r as 1st line treatment.

Total patient sampling of eligible, assenting and consenting adolescents was considered after noting that the clinic had 267 children, adolescents and young adults on boosted protease inhibitors from 0 to 22 years of age, either as 1st or 2nd line treatment. The study was divided into 2 phases:

Phase 1: Eligible participants were randomised to intervention (mDAART + SC) or control (SC + SAT) arms. Randomisation was done using random numbers sealed in opaque envelopes. Questionnaires were administered at baseline and after follow-up. Participants were followed for 90 days. At the end of follow-up, viral load was measured again. Self-reported adherence was measured using AIDS Clinical Trials Group (ACTG) adherence follow-up questionnaire (QLO702) and visual analogue scale (VAS) (Chesney et al., 2000; Walsh et al., 2002).

Phase 2: Participants with continued treatment failure (viral load ≥1 000 copies/ml) had genotypic HIV drug resistance testing.

*Corresponding author. E-mail: tdchawana@gmail.com. Tel: +263 773 276 306.

Components of each arm are summarised in Figure 1. Standard care (SC) consisted of 3 monthly hospital visits to see clinic doctors, adherence counselling by trained peer counsellors and drug refills at each hospital visit. SAT consisted of participants taking medication on their own, with or without supervision by caregivers. The intervention, mDAART, consisted of scheduled home visits during the week and short message service (SMS) on weekends by trained field workers. Home visits and SMS text messages were timed to coincide with the time participant was taking ATV/r. Home visits were scheduled during weekdays only (Mondays to Fridays) as shown in Figure 1. Trained field workers observed participants swallow medication and completed home visit charts. Participants were given a "pill chart" to complete over the 90 days.

Samples for viral load and HIV drug resistance testing were collected in 2×4 ml K-EDTA tubes respectively, gently inverted 8 to 10 times to prevent clotting, transported at atmospheric temperature to the laboratory. The Roche COBAS AmpliPrep/COBAS Taqman HIV-1 Test version 2.0 was used for viral load measurement, with a linear range of 20 to 10,000000 copies/ml. HIV drug resistance mutations were generated by the Celera ViroSeq® HIV-1 genotyping system version 2.0 (Abbott Molecular Diagnostics). Sequencing was done on 3500 Genetic Analyser supplied by Thermo Fisher, Life Technologies. Mutations were identified with ViroSeq software and analysed with the Stanford database (www.HIVDB.stanford.edu) to interpret drug susceptibility.

Ethical approval

This study was approved by Harare hospital institutional review board, Joint Research Ethics Committee (JREC/51/14), Biomedical and Research Training Institute (BRTI) and Medical Research Council of Zimbabwe (MRCZ/A/1840). This clinical trial was registered with Pan African Clinical Trial Registry (PACTR201502001028169) and National Institutes of Health (NIH) Clinical Trials.gov (NCT02689895).

Statistical considerations

Data from questionnaires was entered into research electronic data capture (REDCap), a web-based application (Harris et al., 2009). All data was analysed in Stata version 14 (Stata Corp). Treatment failure was defined as viral load ≥1 000 copies/ml after 90 days follow-up. We used Chi-square (and Fischer's test where appropriate) and student's t test to determine associations between mDAART, standard of care, self-reported adherence and virological suppression (<1 000 copies/ml. P-values are 2-sided and considered statistically significant if <0.05. Primary treatment outcome was defined as viral load <1 000 copies/ml after 90 days of follow-up.

Possible confounders and factors with p<0.25 in bivariate analysis were considered in multivariate analysis to adjust for the effect of mDAART on viral load and self-reported adherence including: age, gender, level of education, orphan and caregiver status; World Health Organisation (WHO) clinical stage at ART initiation; baseline, latest and on-treatment peak CD4 cell counts; time on 1st line, 2nd line and total time on ART; baseline, follow-up and change in viral load; pill burden per day; dosing frequency and body-mass index (BMI)-for-age (World Health Organisation Multicentre Growth Reference Study Group 2007). Stepwise logistic regression was used in multivariate analysis.

RESULTS

Fifty participants were recruited. Of the participants who were screened, 53/108 (49%) were virologically suppressed (viral load <1 000 copies/ml). One hundred and six (98%) participants accepted home visits. Only 2/108 (2%) participants who were eligible refused home visits citing their intrusive nature. Twenty-three (46%) and 27(54%) participants were randomised to intervention and control arms respectively (Figure 2).

Mean age was 15.8 years. Most participants were either in secondary or high school (form 1-6) (78%). There were more females (54%) than males. 46% were double orphans. Only 20% lived with their biological parent(s). At initiation of 1st line ART, 68% had WHO clinical stage 3 or 4 disease, and 42% had a CD4 cell count <200 cells/mm^3. At enrollment into study, 52% had CD4 count <200 cells/mm^3 and 30% had low BMI-for-age (thinness or severe thinness). Eighty-six percent were taking tenofovir/lamivudine (300 mg/300 mg) fixed dose combination (FDC) and ATV/r (300 mg/100 mg) FDC; 90% were taking a total of 2 to 4 ART tablets (including cotrimoxazole prophylaxis) a day; and 90% were taking ART (including cotrimoxazole prophylaxis) once a day. Mean total time on ART was 78 months (Table 1).

Treatment arms were well matched at baseline. Forty percent had average self-reported adherence <80% at baseline compared to 22% after follow-up, and 66% reported an increase in self-reported adherence after follow-up. Average self-reported adherence and ATV/r adherence by visual analogue scale were similar. Mean viral load change was -1.1 $\log_{10}$ copies/ml, 74% had overall decrease in viral load, 46% had ≥1 $\log_{10}$ decrease in viral load and 40% achieved virological suppression (viral load <1 000 copies/ml) (Table 2).

Common reasons for missing ART were simply forgetting (68%), being away from home (62%), problem with keeping time (50%) and falling asleep before taking medication or waking up late (46%) (Figure 3).

52% of the participants in mDAART achieved virological suppression compared to 30% in standard care. There was a modest increase in viral load suppression in mDAART compared to SC after stratifying by viral load <1 000 vs ≥1 000 copies/ml (p=0.105). Viral load decreased more in mDAART arm compared to standard care (p=0.03) and viral load at follow-up was lower in mDAART compared to standard care (p=0.04). Average self-reported adherence in previous 1 month measured by visual analogue scale at follow-up was higher in mDAART compared to standard care (p=0.05), and the number of participants who reported closely following their dosing schedule in the previous 4 days was higher in mDAART compared to standard care at follow-up (p=<0.001) (Table 3).

There were no significant differences between suppressed and unsuppressed participants. Multivariate models were assessed comparing mDAART to SC, fitting self-reported adherence characteristics associated with virological suppression (Table 4).

Participants in mDAART were 90% less likely to report

Figure 1. Components of study arms.

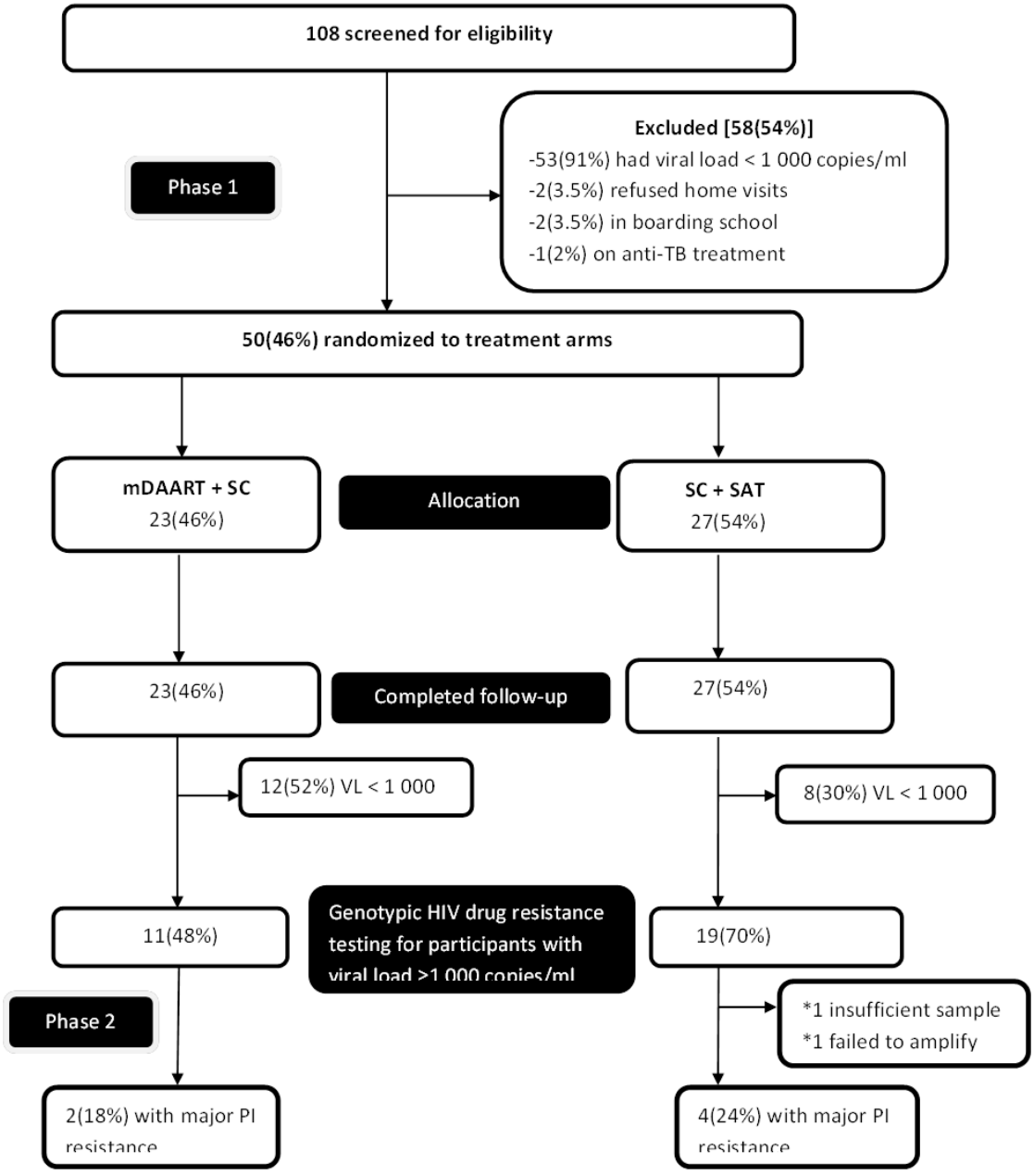

Figure 2. Consort flow chart of participants. *PI, protease inhibitor.*

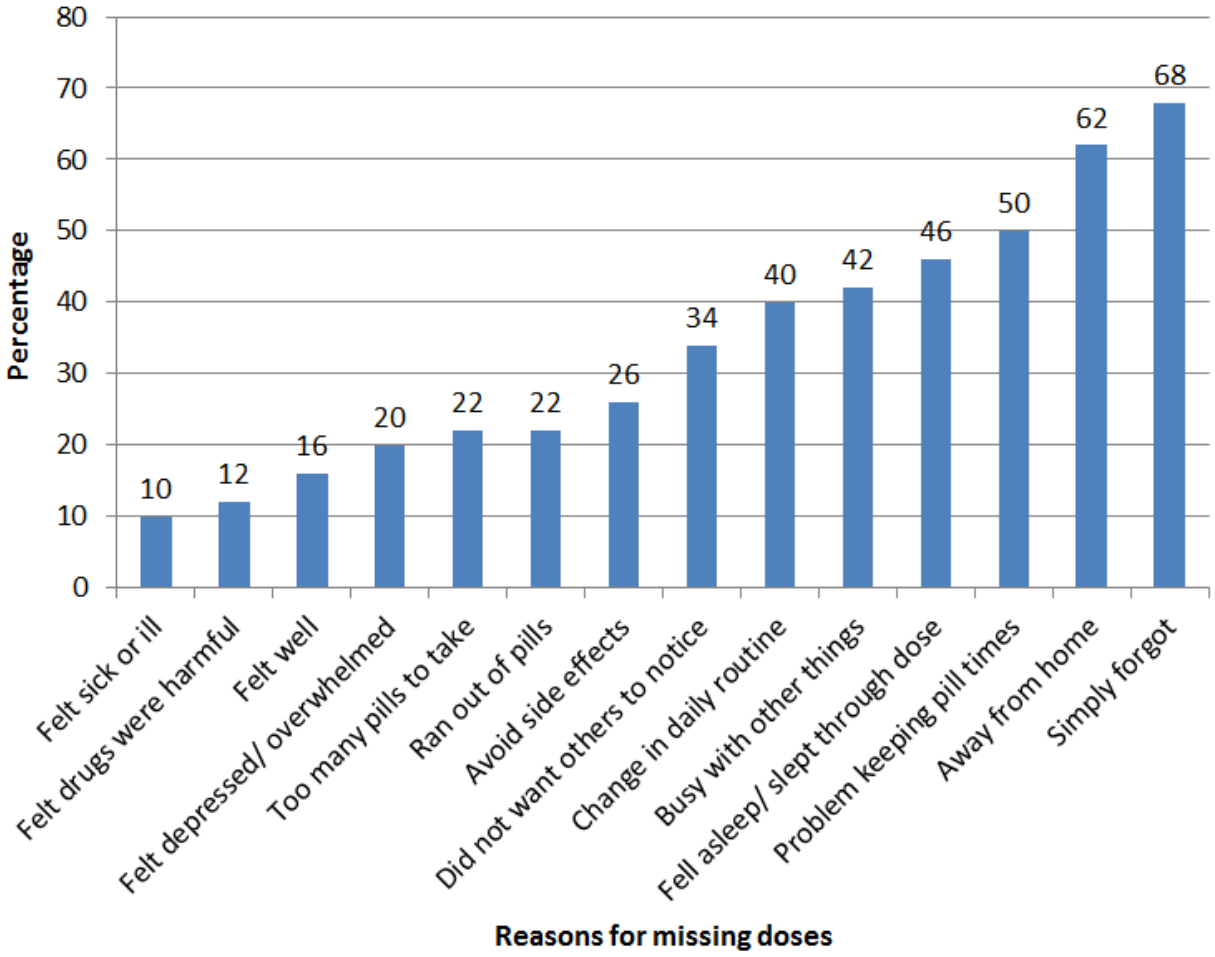

Figure 3. Reasons for missing ART doses.

<80% adherence in the previous 1 month (p=0.023), were 4.8 times more likely to closely follow their dosing schedule in the previous 4 days (p=0.004) compared to those who were not exposed to the intervention (Table 5).

Genotypic HIV drug resistance test

Thirty (60%) participants had viral load ≥1 000 copies/ml at 3 months and 28/30 (93%) had a genotypic HIV drug resistance test within 1 month of follow-up viral load measurement. Three (11%) participants had wild type virus (Table 6). PI resistance was seen in 10(36%). High level atazanavir/ritonavir resistance was detected in 6(21%) of the 28 participants, 5 of whom had intermediate and/or low level ATV/r resistance mutations and 1 had a single I50L mutation. Three (11%) of the 4 participants with multiple PI resistance mutations had high level resistance to ATV/r, lopinavir/ritonavir (LPV/r) and darunavir/ritonavir (DRV/r) (V32I, I50L, I54V, I47V and V82A) and were switched to 3rd line integrase strand transfer inhibitors (InSTI)-based regimens (raltegravir). The other 3 had no resistance to LPV/r, and were switched to LPV/r, which is the available alternative 2nd line treatment (Table 6). The most frequent PI mutations were A71I/T/V (18%), V82A/M (14%), M46I (11%), L10F/V (11%) and I50L (11%) (Figure 4).

DISCUSSION

Directly observed treatment (DOT) has been successfully implemented in anti-TB treatment. However, its use in HIV treatment is controversial. In our study, a short-term mDAART intervention provided to adolescents failing 2nd line treatment was associated with a significantly greater decrease in viral load and increase in self-reported adherence compared to standard care, and it also modestly increased virological suppression. Our findings support earlier findings which found that DAART decreases viral load by an effect size between 20 and 30% and increases self-reported adherence when targeted to at-risk populations (Altice et al., 2004; Altice et al., 2007; Amico et al., 2006; Berg et al., 2011; Ford et

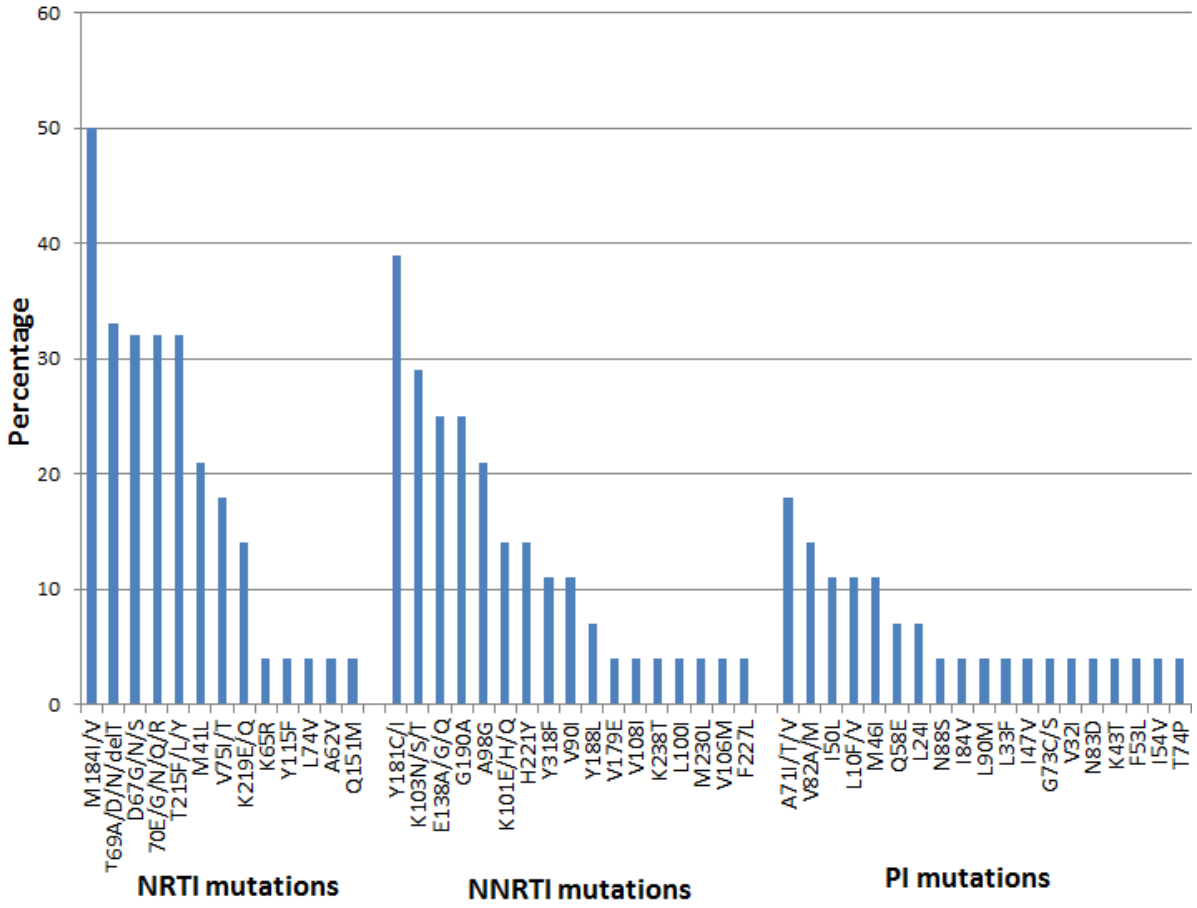

Figure 4. Frequency of HIV drug resistance mutations by ARV drug class.

al., 2009; Goggin et al., 2007; Lucas et al., 2006; Nachega et al., 2010; Wohl et al., 2006). At-risk groups include drug-abusers, patients with poorly controlled mental illness, homeless and marginally housed people.

We also found that 40% of adolescents had adherence <80% at baseline. Adolescent adherence to treatment is lower than that for children and adults (Kim et al., 2014; Sohn and Hazra, 2013). As children grow older, responsibility of HIV care usually shifts from caregiver to adolescent self-management (Modi et al., 2012; Taddeo et al., 2008). This transition usually coincides with complex psycho-social factors typical of this age group at a time of physical and emotional transition to adulthood (Davies et al., 2008; Lowenthal et al., 2014). Moreover, vertically infected adolescents are also likely to have been on ART for longer periods, resulting in treatment fatigue.

Forgetfulness was the most common cited reason for missing doses, and concurs with findings from earlier studies in adults (Barfod et al., 2006; Koole et al., 2016). mDAART allows direct observation of dose ingestion, reminding adolescents to take medication and providing psycho-social support. This increases adherence and decreases viral load if there is no drug resistance and drug exposure is adequate. Interestingly, among the common reasons for missing doses cited, there were no treatment related reasons. This finding is encouraging and supports earlier findings that ATV/r and tenofovir/lamivudine FDCs are tolerable due to favourable side effect profiles, once daily dosing and low pill burden (Achenbach et al., 2011; Dong et al., 2016; Wensing et al., 2010). This allows policy makers to concentrate on addressing psycho-social causes of non-adherence in adolescents.

Acceptance rate for home visits in our study was surprisingly higher than previously reported (Altice et al., 2007; Wohl et al., 2006). This finding is encouraging. Adolescents who are failing 2nd line regimens are often going to school. A community or clinic-based DOT intervention could face challenges in implementation due to busy lifestyles and stigmatisation. A home-based adherence intervention offers lesser burden to adolescents. However, the cost involved in mDAART, the intrusive nature of the intervention, breach of confidentiality of HIV status and migration of participants pose challenges to implementation. If DAART is going to

Table 1. Baseline socio-demographic and treatment characteristics.

Variable	Result (n=50) n(%) or mean(SD); 95% CI
Age (years)	15.8 (1.8); 11 – 18
Gender	
Female	27(54)
Male	23(46)
Current level of education	
Primary	4(8)
Secondary/advanced	39(78)
Other	7(14)
Orphan status	
Non-orphan (both parents alive)	7(14)
Single orphan	20(40)
Double orphan	23(46)
Caregiver	
Parent/s	10(20)
Other (grandparent/s, sibling, aunt/uncle)	40(80)
WHO clinical stage at ART initiation	
1-2	16(32)
3-4	34(68)
CD4 cell count at ART initiation (cells/mm^3)	
<200	21(42)
200-350	9(18)
>350	20(40)
CD4 cell count at enrollment (cells/mm^3)	
<200	26(52)
200-350	12(24)
>350	12(24)
On-treatment peak CD4 cell count (cells/mm^3)	
<200	2(4)
200-350	4(8)
>350	44(88)
Basis of diagnosis of 1^{st} line treatment failure	
Clinical	33(66)
Immunological	47(94)
Virological	28(56)
Time on 1^{st} line ART (months)	55(26); 6-107
Time on 2^{nd} line ART (months)	22(10); 8-66
Total time on ART (months)	78(26); 24-134
Current treatment	
Tenofovir/lamivudine/atazanavir/ritonavir	43(86)
Zidovudine/lamivudine/atazanavir/ritonavir	3(6)
Abacavir/lamivudine/atazanavir/ritonavir	2(4)
Abacavir/didanosine/atazanavir/ritonavir	2(4)
Cotrimoxazole prophylaxis	49(98)
Pill burden per day	
2-4	45(90)
5-6	5(10)
Dosing frequency per day	
Once daily	45(90)
Twice daily	5(10)
BMI-for-age	

Table 1 cont'd

Underweight (severe thinness and thinness)	14(30)
Normal	25(55)
Overweight	7(15)

WHO = World Health Organization; ART= antiretroviral therapy; BMI = body mass index.

Table 2. Treatment characteristics at baseline and after follow-up.

Variable	Baseline (n=50) n(%) or mean(SD); 95% CI	After follow-up (n=50) n(%) or mean(SD); 95% CI
Average self-reported adherence, VAS (%)		
≥95	15(30)	25(50)
80-94	15(30)	14(28)
<80	20(40)	11(22)
ATV/r self-reported adherence, VAS (%)		
≥95	16(32)	28(56)
80-94	15(30)	11(22)
<80	19(38)	11(22)
Change in average self-reported adherence, VAS:		
No change	-	7(14)
Decreased	-	10(20)
Increased	-	33(66)
Missed all doses in a day in past 4 days		
Yes	15(30)	5(10)
No	35(70)	45(90)
Missed at least 1 dose in past 4 days		
Yes	18(36)	18(36)
No	32(64)	32(64)
Closely followed dosing schedule in past 4 days		
Yes	22(44)	29(58)
No	28(56)	21(42)
Missed at least 1 dose previous weekend		
Yes	12(24)	12(24)
No	38(76)	38(76)
Last time a dose/s was missed		
0-4 weeks ago	28(56)	18(36)
>4 weeks ago	22(44)	32(64)
Viral load ($\log_{10}$ copies/ml)	4.8(0.8); 3-7	3.7(1.5); 1.3-5.9
Viral load change ($\log_{10}$ copies/ml)	-	-1.1(1.5); -5.5-2
Viral load change:		
Decreased	-	37(74)
Increased	-	13(26)
≥1 $\log_{10}$ decrease in viral load	-	23(46)
<1 $\log_{10}$ decrease in viral load	-	27(54)
Viral load, copies/ml		
<1 000	-	20(40)
≥1 000		30(60)

VAS, visual analogue scale; ATV/r, atazanavir/ritonavir.

be implemented, there needs to be careful consideration to confidentiality of patients' HIV status, convenience to

Table 3. Comparison of participants' treatment characteristics by treatment arms.

Variable	mDAART (n=23) n(%) or mean(SD); 95% CI	Standard care (n=27) n(%) or mean(SD); 95% CI	p-value
Viral load at follow-up			
<1 000 copies/ml	12(52)	8(30)	0.105
≥1 000 copies/ml	11(48)	19(70)	
Viral load change			
≥1 log_{10} decrease	12(52)	11(41)	0.399
<1 log_{10} decrease	11(48)	16(59)	
Follow-up viral load (log_{10} copies/ml)	3.3(1.5); 2.6-3.9	4(1.5); 3.4-4.6	0.048
Viral load decrease (log_{10} copies/ml)	-1.5(1.6); -2.2- -0.9	-0.8(1.3); -1.3- -0.3	0.031
Average self-reported adherence, (VAS) at follow-up (%)			
≥95	15(65)	10(37)	0.050
80-94	6(26)	8(30)	
<80	2(9)	9(33)	
Change in average self-reported adherence (VAS)			
No change	3(13)	4(15)	0.538
Increased	17(74)	16(59)	
Decreased	3(13)	7(26)	
Missed all doses in a day in past 4 days at follow-up			
Yes	1(4)	4(15)	0.357
No	22(96)	23(85)	
Missed at least 1 dose in past 4 days			
Yes	2(9)	7(26)	0.114
No	21(91)	20(74)	
Closely followed dosing schedule in past 4 days at follow-up			
Yes	19(83)	10(37)	<0.001
No	4(17)	17(63)	
Missed at least 1 dose in previous weekend at follow-up			
Yes	3(13)	3(11)	0.985
No	20(87)	24(89)	
Last time a dose was missed at follow-up			
0-4 weeks ago	7(30)	11(41)	0.449
>4 weeks ago	16(70)	16(59)	

VAS, visual analogue scale.

the patient and flexibility. Community health workers can assume this responsibility as they are familiar with communities they work in and have a portfolio full of other responsibilities (contact tracing for TB, dysentery and other communicable diseases, and health awareness). Use of technology (SMS, automated calls, camera phones and video internet) could reduce the need for many physical home visits. Family members/friends could also observe dose ingestion on days that mDAART will not be done. Once daily ART regimens also ease implementation DAART.

Time on 2nd line ART was shorter than time on 1st line ART in this study. This finding concurs with findings from previous studies, and is worrying. Risk of subsequent treatment failure increases after 1st line failure (Chawana et al., 2014). Adolescents that are failing 2nd line ART are at high risk of failing 3rd line and salvage regimens. Third line regimens are largely unavailable and where they are available, they require HIV drug resistance testing prior to switch to 3rd line (Conradie et al., 2012; Federal Ministry of Health Nigeria, 2010; Ministry of Health Botswana, 2012; National Department of Health, 2012; World Health Organisation (WHO) 2010a; World Health Organisation (WHO) 2010b; World Health Organisation HIV/AIDS Programme, 2013). However, HIV genotypic drug resistance testing is unavailable in public health care in RSL, and is expensive in private laboratories (USD$382 and USD$795), which ship their samples to South Africa. Maintaining adequate adherence in adolescents could reduce the need for expensive 3rd line

Table 4. Comparison by viral load suppression to <1 000 copies/ml after 3 months.

Variable	Viral load <1 000 copies/ml (n=20) n(%) or mean(SD); 95% CI	Viral load ≥1 000 copies/ml (n=30) n(%)or mean(SD); 95% CI	p-value
Age (years)	15(1.98); 14.4-16.3	16(1.66); 15.4-16.7	0.08
Gender:			
Female	10(50)	17(57)	0.643
Male	10(50)	13(43)	
Current level of education			
Primary	2(11)	2(8)	
Secondary/advanced	15(83)	24(92)	0.582
Other	1(6)	0(0)	
Orphan status:			
None	2(10)	5(17)	
Single orphan	8(40)	12(40)	0.858
Double orphan	10(50)	13(43)	
Caregiver:			
Parent/s	3(15)	7(23)	0.470
Other (grandparent/s, sibling, aunt/uncle)	17(85)	23(77)	
WHO clinical stage at ART initiation			
1-2	8(40)	8(27)	0.322
3-4	12(60)	22(73)	
CD4 cell count at ART initiation (cells/mm^3)			
<200	8(40)	13(43)	
200-350	5(25)	4(13)	0.563
>350	7(35)	13(43)	
CD4 cell count at enrollment (cells/mm^3)			
<200	7(35)	19(63)	
200-350	6(30)	6(20)	0.133
>350	7(35)	5(17)	
On treatment peak CD4 cell count (cells/mm^3)			
<200	0(0)	2(7)	
200-350	2(10)	2(7)	0.650
>350	18(90)	26(86)	
Time on 1st line ART (months)	57.3(18.6); 48-62	52.8(30); 41-64	0.281
Time on 2nd line ART (months)	21.8(8.3); 17.8-25.9	22.5(11); 18.3-26.7	0.409
Total time on ART (months)	81.3(17.6); 73-90	75.3(30.8); 63-87	0.217
Dosing frequency per day at follow-up			
Once daily	19(95)	28(93)	1.000
Twice daily	1(5)	2(7)	
BMI-for-age			
Normal	12(63)	13(48)	
Underweight (severe thinness and thinness)	4(21)	10(37)	0.499
Overweight	3(16)	4(15)	
Treatment arm			
mDAART	12(60)	11(37)	0.105
Standard care	8(40)	19(63)	
Average self-reported adherence, (VAS) at follow-up (%)			
≥95	10(50)	15(50)	
80-94	8(40)	6(20)	0.143
<80	2(10)	9(30)	
Change in self-reported adherence (VAS)			

Table 4 cont'd

No change	5(25)	2(7)	0.181
Increased	11(55)	22(73)	
Decreased	4(20)	6(20)	
Missed all doses in a day in past 4 days at follow-up			
Yes	1(5)	4(13)	0.636
No	19(95)	26(87)	
Missed at least 1 dose in past 4 days			
Yes	3(15)	6(20)	0.652
No	17(85)	24(80)	
Closely followed dosing schedule in past 4 days at follow-up			
Yes	14(70)	15(50)	0.160
No	6(30)	15(50)	
Missed at least 1 dose in previous weekend at follow-up			
Yes	3(15)	3(10)	0.672
No	17(85)	27(90)	
Last time a dose was missed at follow-up			
0-4 weeks ago	7(35)	11(37)	0.904
>4 weeks ago	13(65)	19(63)	

mDAART, modified directly administered antiretroviral therapy; VAS, visual analogue scale.

Table 5. Multivariate logistic regression comparing mDAART referenced to standard care.

Variable	Relative risk (95% confidence interval)	p Value
Average self-reported adherence, (VAS) at follow-up (%)		
≥95	-	-
80-94	0.4(0.1-1.5)	0.162
<80	0.1(0.02-0.8)	0.023
Closely followed dosing schedule in past 4 days at follow-up		
No	-	-
Yes	4.8(1.6-13.8)	0.004

treatment and HIV drug resistance testing.

Nearly one-fifth of participants demonstrated high level ATV/r resistance, and was the same as that found in adults (Boender et al., 2016). This finding contradicts previous studies which found that patients on boosted PIs who develop virological treatment failure do not have clinically significant PI mutations and they re-suppress after intensive adherence interventions (Garone et al., 2014; Levison et al,. 2012). Although ATV/r has high genetic barrier against resistance, perinatally infected adolescents often have long treatment histories, inconsistent treatment adherence and multi-drug experience resulting from numerous switches when treatment failure has occurred, all favouring evolution of drug resistance (MacDonell et al., 2013). This finding is extremely worrying due to limited supply of 3rd line regimens in RSL. Beyond 2nd line treatment, prognosis is poor. Persistence of high level NNRTI resistance in this study is also worrying because it rules out the possibility of future use of this drug class in the event that patients run out of treatment options.

Conclusion

Administering a home-based DAART intervention with direct observation of dose ingestion and SMS reminders to adolescents who were failing 2nd line treatment increased self-reported adherence and decreased viral load. High level PI resistance was also demonstrated. We recommend that HIV drug resistance testing and 3rd line antiretroviral treatment, like darunavir/ritonavir and raltegravir, be made more available in RSL in anticipation of a surge in PI resistance. We also propose that HIV drug resistance testing be done at time of diagnosis of 2nd line treatment failure. Waiting 3 to 6 months for a 2nd

Table 6. Resistance mutations by ARV drug class.

Participant	Protease inhibitor mutations	NRTI mutations	NNRTI mutations
1	L10F, *M46I*, Q58E, A71I, I84V*	M41L, D67G, T69N, K70N, V75I, M184V*, T215F	A98G, *V179E*, Y181C*, G190A*
2	I50L*	M41L, D67G, V75I, M184V/I*, K70Q, T215F	Y188L*
3	Q58E, V82M	D67G, M184V*, T69D, K70R, K219Q	A98G, Y181C*, G190A*, K101E
4	-	D67G, K70R, T215I, T219E	G190A*, E138G
5	-	-	A98G, Y181C*, V90I
6	-	-	-
7	-	-	*K101H/Q*
8	-	M184V*	K103N*, *E138A*
9	-	-	-
10	-	D67G, M184V*, K70G	A98G, Y318F
11	-	T69N	Y181C*, G190A*, K101E, V90I
12	-	-	Y181C*, K103T, H221Y
13	-	V75I, M184V*, K65R*, D67N, Y115F, K219E	Y181C*, V108I
14	A71T	M41L, T69N, K70R, D67N, T215L, K219E	A98G, Y181C*, K103N*, K238T
15	-	M184V*, K70E/G/R, D67N	V90I, K103N*, Y318F
16	-	M184I/V*	G190A*
17	*L90M*	T69N	-
18	-	M41L, M184V*, T215C/Y	K103N*, Y318F, E138Q
19	-	M41L, V75I, M184V*, T215F/Y	*E138A*, H221Y, Y181I
20	A71I/T, N88S*, L10V	T69A/N, M184V*, T215F, K70R, K219E, D67S, L74V	K103N*, L100I*, M230L*
21	-	T69D/N	Y181C*, G190A*
22	-	T69N	Y181C*
23	-	-	-
24	*M46I*, I50L*, L10V, L33F, *I47V*, A71V, G73C/S, V82A[#]	M184V*, T215F	A98G, G190A*, K101E, *E138A*
25	*M46I*	-	Y181C*, E138G, H221Y
26	I50L*, V82M, V32I[#], L24I, N83D	M41L, K70N, V75I, M184V*, T215Y	H221Y, K103S*, V106M*, F227L[#]
27	V82M, A71V, L24I, K43T, F53L, I54V[#], T74P	M184V*, A62V, 69delT, V75T, Q151M	Y188L*
28	-	-	K103N*, *E138A*
Without mutations, n(%)	18(64)	8(29)	4(14%)

***** high level resistance; [#]intermediate level resistance; Italics- low level resistance; PI, protease inhibitor; NNRTI, non-nucleotide reverse transcriptase inhibitors; NRTI, nucleot/side reverse transcriptase inhibitors.

viral load results in disease progression and creates a window for spread of PI resistant virus.

Limitations

The mDAART intervention was based on SMS reminders and observation of dose ingestion. It is therefore difficult to separate the effect of each component. Future studies could separate these 2 components and compare their effects individually. In addition, frequency of home visits were intensive at the beginning and reduced with time, therefore their effect might have waned off as the visits reduced. The intervention was administered for 3 months,

which is relatively short. There was no follow-up after the intervention was discontinued to see if the effect of mDAART would be sustained. Measurement of adherence using self-reports is known to overestimate adherence due to recall bias and social desirability. Even in the presence of adequate adherence, drug exposure may be inadequate (such as in chronic gastroenteritis and increased drug clearance in enzyme induction), resulting in treatment failure. Our sample was also small for power to be adequate.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript. Preliminary results were presented as a poster at the AIDS 2016 conference in Durban.

ACKNOWLEDGEMENTS

The author would like to thank Dr Rashida Ferrand for helping with study conceptualisation; Dr Hildah Mujuru for providing guidance; Dr Monica Gandhi for critically revising and editing the protocol; Harare hospital adolescent patients and staff for participating; Child Protection Society for providing trained field workers for home visits; the research nurse, Noleen Chifamba; and Departments of Clinical Pharmacology and Paediatrics, College of Health Sciences of University of Zimbabwe for providing supervision and guidance.

Funding

This study was funded by University of Zimbabwe Staff Development Fellowship (SDF), Fogarty HIV Implementation Science Research Training Program (FHISRTP) (1D43TW009539-03) and Fogarty International Clinical, Operational and Health Services Research and Training Award (ICOHRTA) (2U2RTW007367-01). The contents of this publication are solely the responsibility of the authors, and do not represent the views of the funders.

REFERENCES

Achenbach CJ, Darin KM, Murphy RL, Katlama C (2011). Atazanavir/Ritonavir-Based Combination Antiretroviral Therapy for treatment of HIV-1 Infection In Adults. Future Virol. 6(2):157-177.

Altice FL, Maru DS, Bruce RD, Springer SA, Friedland GH (2007). Superiority Of Directly Administered Antiretroviral Therapy Over Self-Administered Therapy Among HIV-Infected Drug Users: A Prospective, Randomized, Controlled Trial. Clin. Infect. Dis. 45(6):770-778.

Altice FL, Mezger JA, Hodges J, Bruce RD, Marinovich A, Walton M, Springer SA, Friedland GH (2004). Developing A Directly Administered Antiretroviral Therapy Intervention For HIV-Infected Drug Users: Implications For Program Replication. Clin. Infect. Dis. 38(S5):S376-S387.

Amico KR, Harman JJ, Johnson BT (2006). Efficacy Of Antiretroviral Therapy Adherence Interventions: A Research Synthesis Of Trials, 1996 To 2004. J. Acquir. Immune. Defic. Syndr. 41(3):285-297.

Barfod TS, Sorensen HT, Nielsen H, Rodkjaer L, Obel N (2006). 'Simply Forgot' Is The Most Frequently Stated Reason For Missed Doses of HAART Irrespective of degree of adherence. HIV Med. 7(5):285-290.

Berg KM, Litwin A, Li X, Heo M, Arnsten JH (2011). Directly Observed Antiretroviral Therapy Improves Adherence And Viral Load In Drug Users Attending Methadone Maintenance Clinics: A Randomized Controlled Trial. Drug Alcohol Depend. 113(2-3):192-199.

Boender TS, Hamers RL, Ondoa P, Wellington M, Chimbetete C, Siwale M, Labib Maskimos EEF, Balinda SN, Kityo CM, Adeyemo TA, Akanmu AS, Mandaliya K, Botes ME, Stevens W, Rinke De Wit TF, Sigaloff KCE (2016). Protease Inhibitor Resistance In The First 3 Years Of Second-Line Antiretroviral Therapy For HIV-1 In Sub-Saharan Africa. J. Infect. Dis. 214:873-883.

Chawana T, Reid A, Bwakura T, Gavi S, Nhachi C (2014). Factors Influencing Treatment Failure In HIV Positive Adult Patients on First-Line Antiretroviral Therapy. Cent. Afr. J. Med. 60:5-8.

Chesney MA, Ickovics JR, Chambers DB, Gifford AL, Neidig J, Zwickl B, Wu AW (2000). Self-Reported Adherence to Antiretroviral Medications among Participants in HIV Clinical Trials: The AACTG Adherence Instruments. Patient Care Committee & Adherence Working Group of The Outcomes Committee Of The Adult AIDS Clinical Trials Group (AACTG). AIDS Care 12(3):255-266.

Conradie F, Wilson D, Basson A, De Oliveira T, Hunt G, Joel G, Papathanasopoulos M, Preiser W, Klausner J, Spencer D, Stevens D, Venter F, Van Vuuren C, Levin L, Meintjes G, Orrell C, Sunpath H, Rossouw T, Van Zyl G, Southern Africa HIV Clinicians Society (2012). The 2012 Southern Africa ARV Drug Resistance Testing Guidelines. South Afr. J. HIV Med. 13(4):162-167.

Davies MA, Boulle A, Fakir T, Nuttall J, Eley B (2008). Adherence To Antiretroviral Therapy In Young Children In Cape Town, South Africa, Measured By Medication Return And Caregiver Self-Report: A Prospective Cohort Study. BMC Pediatr. 8:34.

Dong BJ, Ward DJ, Chamberlain LA, Reddy YS, Ebrahimi R, Flaherty JF, Owen WF (2016). Safety And Effectiveness Of Tenofovir/Emtricitabine Or Lamivudine Plus Ritonavir Boosted Atazanavir In Treatment Experienced HIV Infected Adults At Two Urban Private Medical Practises. J. Antivir. Antiretrovir. 4:1-5.

Federal Ministry of Health Nigeria (2010). National Guidelines for HIV and AIDS Treatment And Care In Adolescents And Adults 2010. Abuja, Nigeria.

Ferrand R, Lowe S, Whande B, Munaiwa L, Langhaug L, Cowan F, Mugurungi O, Gibb D, Munyati S, Williams BG, Corbett EL (2010). Survey of Children Accessing HIV Services In A High Prevalence Setting: Time For Adolescents To Count? Bull. World Health Organ. 88(6):428-434.

Ford N, Nachega JB, Engel ME, Mills EJ (2009). Directly Observed Antiretroviral Therapy: A Systematic Review And Meta-Analysis Of Randomised Clinical Trials. Lancet 374(9707):2064-2071.

Garone D, Conradie K, Patten G, Cornell M, Goemaere E, Kunene E, Kerschberger B, Ford N, Boulle A, Van Cutsen G (2014). High Rate Of Virologic Re-Suppression Among Patients Failing Second-Line Antiretroviral Therapy Following Enhanced Adherence Support: A Model of Care In Khayelitsha, South Africa. South African J. HIV Med. 14(4):166-169.

Goggin K, Liston RJ, Mitty JA (2007). Modified Directly Observed Therapy For Antiretroviral Therapy: A Primer From The Field. Public Health Rep. 122(4):472-481.

Gupta RK, Jordan MR, Sultan BJ, Hill A, Davis DH, Gregson J, Sawyer AW, Hamers RL, Ndembi N, Pillay D, Bertagnolio S (2012). Global Trends In Antiretroviral Resistance In Treatment-Naive Individuals With HIV After Rollout Of Antiretroviral Treatment In Resource-Limited Settings: A Global Collaborative Study And Meta-Regression Analysis. Lancet 380(9849):1250-1258.

Harris PA, Taylor R, Thielke R, Payre J, Gonzalez N, Conde JG (2009). Research Electronic Data Capture- A Metadata-Driven Methodology And Workflow Process For Providing Translational Research Informatics Support. J. Biomed. Inform. 42(2):377-381.

Hosseinipour MC, Gupta RK, Van Zyl G, Eron JJ, Nachega JB (2013). Emergence of HIV Drug Resistance During First- And Second-Line Antiretroviral Therapy In Resource-Limited Settings. J. Infect. Dis. 207(S2):S49-S56.

Kim SH, Gerver SM, Fidler S, Ward H (2014). Adherence to Antiretroviral Therapy In Adolescents Living With HIV: Systematic Review And Meta-Analysis. AIDS 28(13):1945-1956.

Koole O, Denison JA, Menten J, Tsui S, Wabwire-Mangen F, Kwesigabo G, Mulenga M, Auld A, Agolory S, Mukadi YD, Van Praag E, Torpey K, Williams S, Kaplan J, Zee A, Babgsberg DR, Colebunders R (2016). Reasons for Missing Antiretroviral Therapy: Results from a Multi-Country study in Tanzania, Uganda and Zambia. PlosOne 11(1): E0147309.

Lessells RJ, Avalos A, De Oliveira T (2013). Implementing HIV-1 Genotypic Resistance Testing In Antiretroviral Therapy Programs in Africa: Needs, Opportunities, and Challenges. AIDS Rev. 15(4):221-229.

Levison JH, Orrell C, Gallien S, Kuritzkes DR, Fu N, Losina E, Freedberg, KA, Wood R (2012). Virologic Failure of Protease Inhibitor-Based Second-Line Antiretroviral Therapy Without Resistance In A Large HIV Treatment Program In South Africa. PlosOne 7(3):E32144.

Lowenthal ED, Bakeera-Kitaka S, Marukutira T, Chapman J, Goldrath K, Ferrand RA (2014). Perinatally Acquired HIV Infection In Adolescents From Sub-Saharan Africa: A Review Of Emerging Challenges. Lancet Infect. Dis. 14(7):627-639.

Lucas GM, Mullen BA, Weidle PJ, Hader S, Mccaul ME, Moore RD (2006). Directly Administered Antiretroviral Therapy In Methadone Clinics Is Associated With Improved HIV Treatment Outcomes, Compared With Outcomes Among Concurrent Comparison Groups. Clin. Infect. Dis. 42(11):1628-1635.

Macdonell K, Naar-King S, Huszti H, Belzer M (2013). Barriers to Medication Adherence In Behaviorally and perinatally infected Youth Living With HIV. AIDS Behav. 17(1):86-93.

Ministry of Health Botswana 2012. Botswana National HIV And AIDS Treatment Guidelines 2012. Republic Of Botswana.

Modi AC, Pai AL, Hommel KA, Hood KK, Cortina S, Hilliard ME, Guilfoyle SM, Gray WN, Drotar D (2012). Pediatric Self-Management: A Framework for Research, Practice, and Policy. Pediatrics 129(2):E473-E485.

Nachega JB, Hislop M, Nguyen H, Dowdy DW, Chaisson,RE, Regensberg L, Cotton M, Maartens G (2009). Antiretroviral Therapy Adherence, Virologic And Immunologic Outcomes In Adolescents Compared With Adults In Southern Africa. J. Acquir. Immune. Defic. Syndr. 51(1): 65-71.

Nachega JB, Mills EJ, Schechter M (2010). Antiretroviral Therapy Adherence and Retention In Care In Middle-Income And Low-Income Countries: Current Status Of Knowledge And Research Priorities. Curr. Opin. HIVAIDS 5(1):70-77.

National Department of Health South Africa (2012). Clinical Guidelines for the Management of HIV And AIDS In Adults And Adolescents. Pretoria, South Africa.

Nglazi MD, Kranzer K, Holele P, Kaplan R, Mark D, Jaspan H, Lawn SD, Wood R, Bekker LG (2012). Treatment Outcomes In HIV-Infected Adolescents Attending A Community-Based Antiretroviral Therapy Clinic In South Africa. BMC Infect. Dis. 12:21**.**

Panel on Antiretroviral Guidelines for Adults and Adolescents (2012). Guidelines for the Use of Antiretroviral Agents In HIV-1 Infected Adults And Adolescents. Department of Health and Human Services (DHHS) 2012.

Panel on Antiretroviral Therapy And Medical Management Of HIV-1 Infected Children (2012). Guidelines for The Use Of Antiretroviral Agents In Paediatric HIV Infection. Department of Health and Human Services (DHHS) 2012.

Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, Wagener MM, Singh N (2000). Adherence to Protease Inhibitor Therapy And Outcomes In Patients With HIV Infection. Ann. Intern. Med. 133(1):21-30.

Rhee SY, Jordan MR, Raizes E, Chua A, Parkin N, Kantor R, Van Zyl GU, Mukui I, Hosseinipour MC, Frenkel, LM, Ndembi N, Hamers RL, Rinke De Wit TF, Wallis CL, Gupta RK, Fokam J, Zeh C, Schapiro JM, Carmona S, Katzenstein D, Tang M, Aghokeng AF, De Oliveira T, Wensing AM, Gallant JE, Wainberg MA, Richman DD, Fitzgibbon JE, Schito M, Bertagnolio S, Yang C, Shafer RW (2015). HIV-1 Drug Resistance Mutations: Potential Applications for Point-Of-Care Genotypic Resistance Testing. PlosOne 10(12):E0145772.

Roux P, Kouanfack C, Cohen J, Marcellin F, Boyer S, Delaporte E, Carrieri P, Laurent C, Spire B (2011). Adherence to Antiretroviral Treatment In HIV-Positive Patients In The Cameroon Context: Promoting The Use Of Medication Reminder Methods. J. Acquir. Immune. Defic. Syndr. 57(S1):S40-S43.

Shuter J (2008). Forgiveness of Non-Adherence to HIV-1 Antiretroviral Therapy. J. Antimicrob. Chemother. 61(4): 769-773.

Shuter J, Sarlo JA, Kanmaz TJ, Rode RA, Zingman BS (2007). HIV-Infected Patients Receiving Lopinavir/Ritonavir-Based Antiretroviral Therapy Achieve High Rates Of Virologic Suppression Despite Adherence Rates Less Than 95%. J. Acquir. Immune. Defic. Syndr. 45(1): 4-8.

Sohn AH, Hazra R (2013). The Changing Epidemiology Of The Global Paediatric HIV Epidemic: Keeping Track Of Perinatally HIV-Infected Adolescents. J. Int. AIDS Soc. 16(1):18555.

Suaysod R, Ngo-Giang-Huong N, Salvadori N, Cressey TR, Kanjanavanit S, Techakunakorn P, Krikajornkitti S, Srirojana S, Laomanit L, Chalermpantmetagul S, Lallemant M, Le CS, Mcintosh K, Traisathit P, Jourdain G (2015). Treatment Failure in HIV-Infected Children On Second-Line Protease Inhibitor-Based Antiretroviral Therapy. Clin. Infect. Dis. 61(1):95-101.

Taddeo D, Egedy M, Frappier JY (2008). Adherence to treatment in adolescents. Paediatr. Child Health 13(1):19-24.

Tang MW, Shafer RW (2012). HIV-1 Antiretroviral Resistance: Scientific Principles and Clinical Applications. Drugs 72(9):E1-25.

Walsh JC, Mandalia S, Gazzard BG (2002). Responses To A 1 Month Self-Report On Adherence To Antiretroviral Therapy Are Consistent With Electronic Data And Virological Treatment Outcome. AIDS 16(2):269-277.

Wensing AM, Van Maarseveen NM, Nijhuis M (2010). Fifteen Years Of HIV Protease Inhibitors: Raising The Barrier To Resistance. Antiviral Res. 85(1):59-74.

World Health Organization (WHO) (2011). Joint United Nations Programme On HIV/AIDS (UNAIDS), United Nations International Childrens' Emergency Fund (UNICEF) (2011). Global HIV/AIDS Response: Epidemic Update and Health Sector Progress Towards Universal Access. 2011 Progress Report Geneva, Switzerland: World Health organization; 2011.

Wohl AR, Garland WH, Valencia R, Squires K, Witt MD, Kovacs A, Larsen R, Hader S, Anthony MN, Weidle PJ (2006). A Randomized Trial of Directly Administered Antiretroviral Therapy And Adherence Case Management Intervention. Clin. Infect. Dis. 42(11):1619-1627.

World Health organization (WHO) (2014). Adolescent HIV Testing, Counselling And Care: Implementation Guidelines For Health Providers And Planners. Geneva, Switzerland.

World Health organization (WHO) (2010a). Antiretroviral Therapy For HIV Infection In Adults And Adolescents: Recommendations For A Public Health Approach (2010 Revision). Geneva, Switzerland.

World Health organization (WHO) (2010b). Antiretroviral Therapy For HIV Infection In Infants And Children: Recommendations For A Public Health Approach (2010 Revision). Geneva, Switzerland.

World Health organization (WHO) HIV/AIDS Programme (2013). Consolidated Guidelines On The Use Of Antiretroviral Drugs For Treating And Preventing HIV Infection. Recommendations For A Public Health Approach.

World Health organization (WHO) Multicentre Growth Reference Study Group (2007). WHO Child Growth Standards Based On Length/Height, Weight And Age. Acta Paediatr. 95(S450):76-85.

Related Journals Published by Academic Journals

- *Clinical Reviews and Opinions*
- *Journal of Cell Biology and Genetics*
- *Journal of Clinical Medicine and Research*
- *Journal of Diabetes and Endocrinology*
- *Journal of Medical Genetics and Genomics*
- *Medical Case Studies*

academicJournals